CHAPTER FOUR

C-H Bond Functionalizations with Palladium(II): Intramolecular Annulations of Arenes

4.1 Introduction

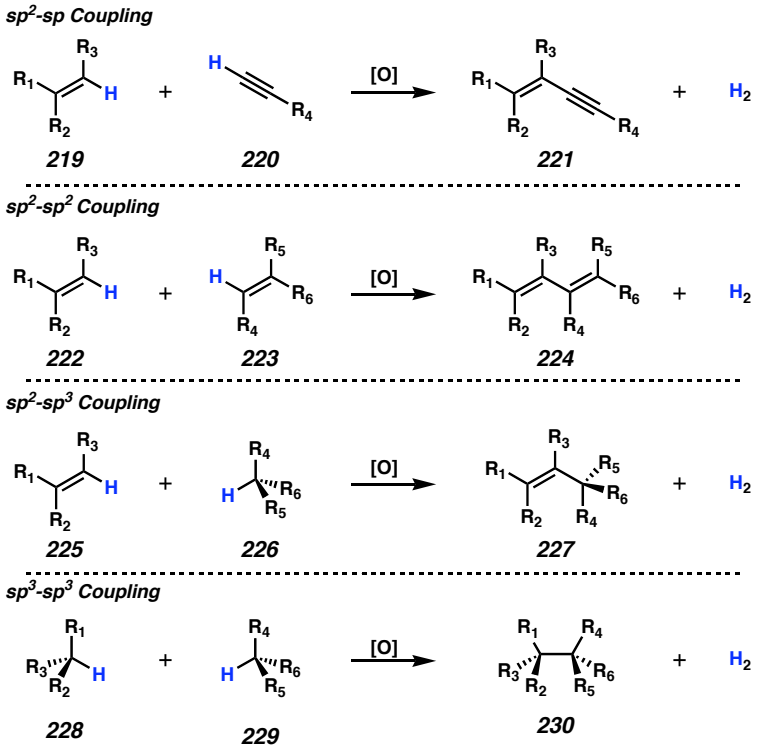
As detailed in Chapters 2 and 3, the development of palladium(II) oxidative transformations that do not involve heteroatom transfer was a principal focus of our research. We had discovered and developed the oxidative kinetic resolution of secondary alcohols using a palladium/sparteine/O_2 system.[1] This oxidative system was then used as a starting point for the development of oxidative heterocyclization reactions in both the racemic and enantioselective sense.[2] It was anticipated that our understanding of these systems could be applied to the development of novel oxidative transformations. Specifically, we sought to extend the palladium/ligand/O_2 catalytic oxidation system to C-C bond forming reactions.

4.1.1 Carbon-Carbon Bond Forming Reactions via Palladium Catalysis

Palladium(0)-catalyzed carbon-carbon bond forming reactions have been well-established in synthetic chemistry.[3] Processes such as the Heck reaction,[4] Stille and Suzuki couplings,[5,6] and the Sonogashira reaction[7] have been widely used for the efficient construction of carbon-carbon bonds. All of these transformations are initiated by the oxidative addition of a palladium(0) catalyst to a carbon-halogen bond, the byproducts of these reactions being either HX (for the Heck and Sonogashira reactions) or MX (for the cross-coupling reactions).

Comparatively, dehydrogenative carbon-carbon bond forming reactions have seen little use in synthetic chemistry. A number of oxidative transformations that can be envisioned by such a process are depicted in Figure 4.1.1. These transformations result in the functionalization of two C-H bonds and the formation of a new C-C bond. Carbons of any hybridization (*sp*, sp^2, or sp^3) can be viewed as coupling partners for these dehydrogenative bond forming reactions.

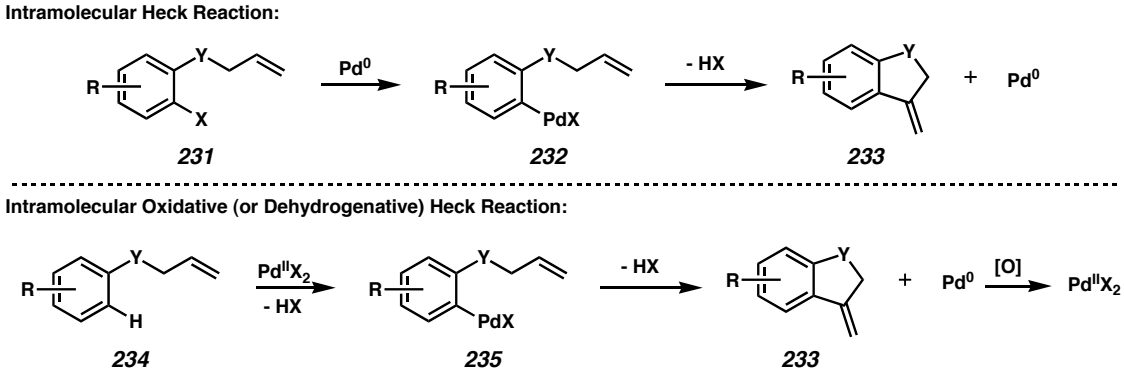
Figure 4.1.1 Oxidative carbon-carbon bond forming reactions.



As a starting point, we decided to investigate intramolecular dehydrogenative couplings between two sp^2 carbons. A reaction of this type is directly analogous to the intramolecular Heck reaction, wherein a halogenated arene (**231**) undergoes an oxidative addition by palladium(0), followed by olefin insertion and β-hydride elimination (Scheme 4.1.1). In a dehydrogenative version, a C-H bond of an arene is directly

functionalized by palladium(II), leading to a similar aryl-palladium intermediate (**235**). The reaction then proceeds in the same fashion as the Heck reaction. This oxidative coupling can be considered more efficient, obviating the need to first install the halide functionality required for a Heck process. Described herein are our efforts toward this goal, culminating in the palladium-catalyzed oxidative annulations of indoles and the syntheses of benzofuran and dihydrobenzofuran derivatives, all involving a C-H bond functionalization event.[8]

Scheme 4.1.1



4.2 Background

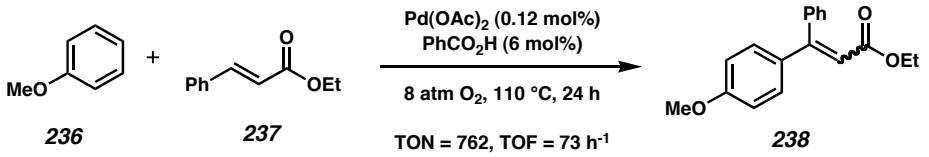
High C-H bond strengths (e.g., methane: 105 kcal/mol; benzene: 110 kcal/mol) significantly limit their reactivity toward functionalization. Despite this barrier, a massive effort has been put forth over the past twenty-five years toward transition metal activation of C-H bonds.[9] One successful reaction manifold is the oxidative coupling of an arene and an olefin by palladium(II), pioneered by Fujiwara.[10] Although successful in several intermolecular cases, examples of intramolecular reactions are rare. We postulated that the aerobic oxidative systems we had been studying could be utilized in

intramolecular C-C bond forming reactions between an arene and an olefin that involve an initial C-H bond functionalization.

4.2.1 Palladium(II) Oxidative Arene-Olefin Couplings

The first aerobic palladium-catalyzed C-C bond forming reaction was reported by Shue in 1971.[11] Benzene and styrene were coupled in the presence of $Pd(OAc)_2$ and approximately 20 atm O_2 at 100 °C to provide stilbene. Up to 110 catalytic turnovers were observed under these conditions. More recently, Jacobs has described a similar system in the oxidative coupling of benzene derivatives and activated esters (Scheme 4.2.1).[12] In the presence of $Pd(OAc)_2$ and a cocatalytic amount of benzoic acid under approximately 8 atm O_2, benzene derivatives could be oxidatively coupled to afford styrenyl compounds. Under these conditions, turnover number and turnover frequency were both remarkably high.

Scheme 4.2.1

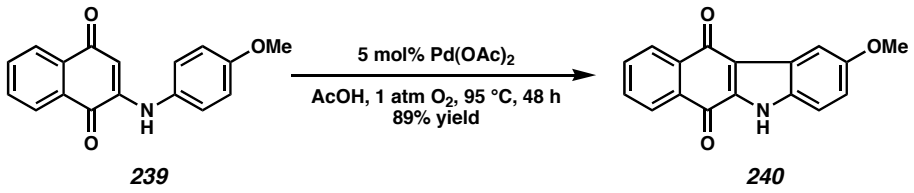


236 *237* *238*

Oxidative C-C bond forming reactions using oxygen as the sole stoichiometric oxidant almost exclusively involved intermolecular examples wherein a solution of an activated olefin (e.g., acrylate esters) in neat arene was stirred under high pressures of oxygen. One notable exception was reported by Åkermark in 1999 (Scheme 4.2.2).[13] Arylaminoquinone **239** was oxidatively cyclized under catalytic $Pd(OAc)_2$ and 1 atm O_2

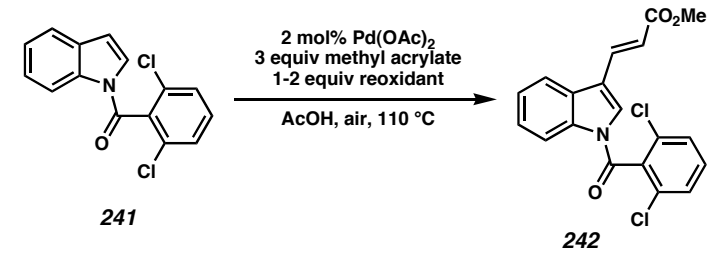
in AcOH at 95 °C to afford product **240**, resembling the core structures of a number of natural products (e.g., murrayquinone A and kinamycin A).

Scheme 4.2.2



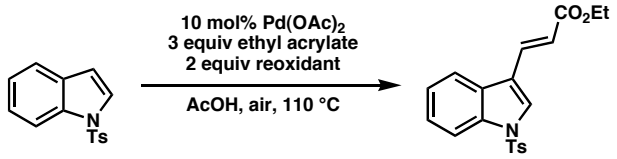
Palladium-mediated oxidative coupling reactions involving the indole nucleus have been studied extensively by Itahara and coworkers.[14] Catalytic examples, however, were consistently plagued by low yields (Scheme 4.2.3). *N*-2,6-Dichlorobenzoylindole (**241**) was oxidatively coupled with methyl acrylate by catalytic $Pd(OAc)_2$ and a number of stoichiometric oxidants (e.g., AgOAc, $Cu(OAc)_2$, $Na_2S_2O_8$, and $NaNO_2$),[14a] but the yield never exceeded 20% in these systems. Alternatively, the oxidative coupling of *N*-tosylindole (**243**) was examined, in this case with higher catalyst loadings.[14b] Although the yields were marginally improved (up to 42%), they were still not particularly useful synthetically. Fujiwara recently described a single example of a catalytic intermolecular oxidative coupling using the indole nucleus.[15] Under $Pd(OAc)_2$ and a benzoquinone/TBHP reoxidation system, indole (**245**) was coupled to methyl acrylate to provide **246** in 52% yield.

Scheme 4.2.3



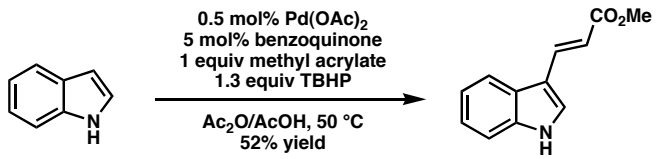
241 242

Reoxidant	TON	Yield (%)
stoich. $Pd(OAc)_2$	--	25
AgOAc	8.8	18
$Cu(OAc)_2$	5.2	10
$Na_2S_2O_8$	3.2	6
$NaNO_2$	3.4	7



243 244

Reoxidant	TON	Yield (%)
stoich. $Pd(OAc)_2$	--	48
AgOAc	3.2	31
$Cu(OAc)_2$	4.1	41
$Na_2S_2O_8$	4.2	42
$NaNO_2$	1.6	16

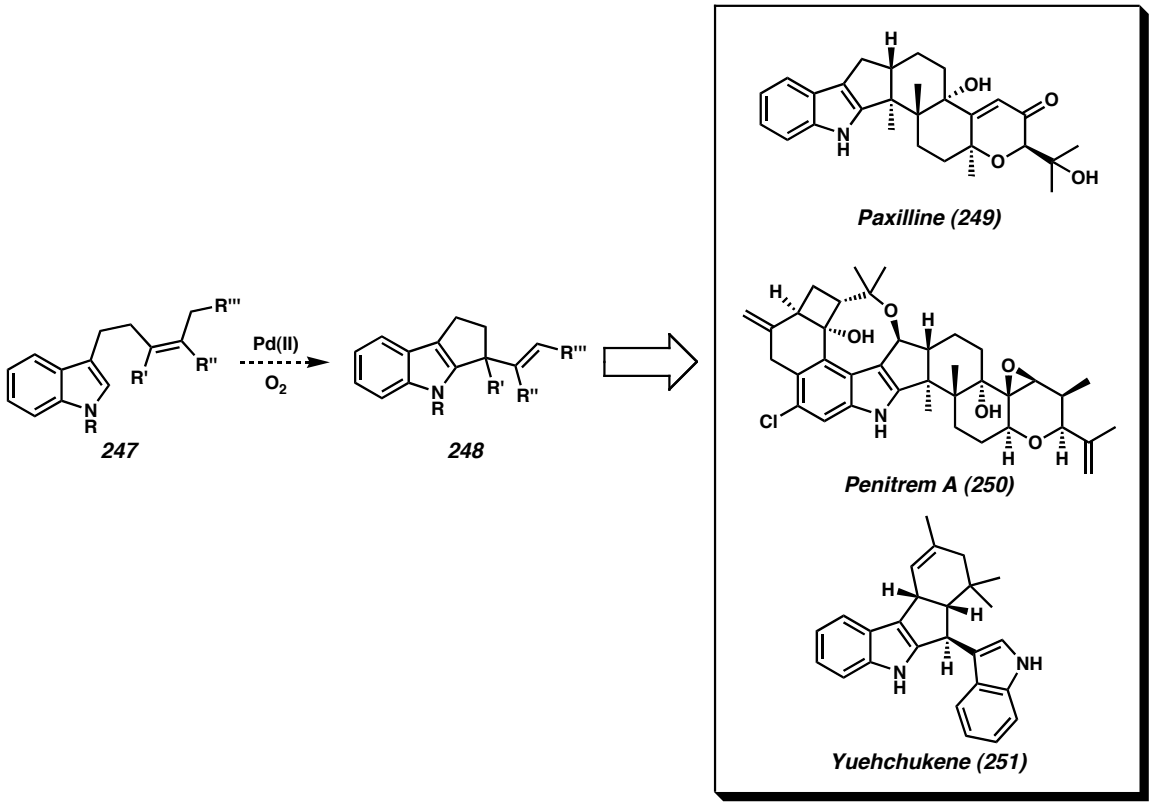


245 246

4.2.2 Synthetic Importance of Annulated Indoles

Although some success has been achieved in oxidative couplings involving the indole nucleus, intramolecular catalytic examples have never been reported. In a general reaction scheme, indole **247** would cyclize onto a tethered olefin to afford annulated indole **248** (Scheme 4.2.4). A reaction of this type would be immensely useful to the synthetic community. Several biologically active natural products (e.g., paxilline,[16] penitrem A,[17] and yuehchukene[18]) containing the core annulated indole structural motif could be accessed by such a reaction.

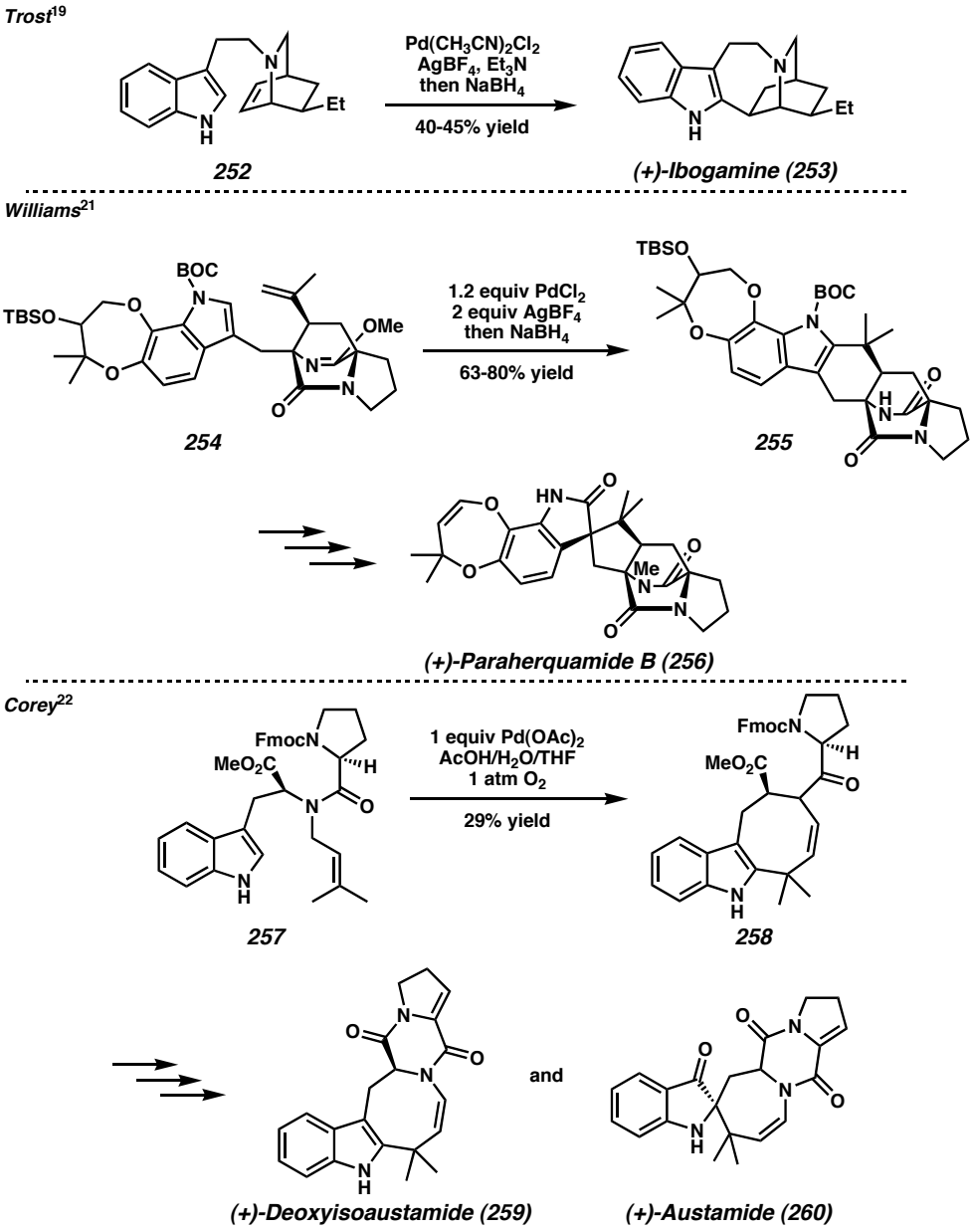
Scheme 4.2.4



We were not the first to recognize the potential utility of an intramolecular indole annulation in natural product synthesis. In 1978, Trost reported the palladium-mediated cyclization and subsequent reduction of indole **252** to produce (+)-ibogamine.[19,20] Fifteen years later, Williams described the total synthesis of paraherquamide B using a similar palladium(II)-promoted cyclization/reduction sequence of indole **254** as the key transformation.[21] More recently, Corey has reported the oxidative cyclization of indole **257** using palladium(II) in the syntheses of members of the austamide class of natural products.[22,23] Although the cyclizations were all effective in the synthetic context, they all required stoichiometric amounts of palladium(II) salts. By comparison, the catalytic palladium/pyridine/O_2 system we had been studying had proven quite effective in a

number of oxidative transformations. We therefore sought to extend this system to catalytic C-C bond forming reactions, specifically oxidative indole annulations.[24,25]

Scheme 4.2.5

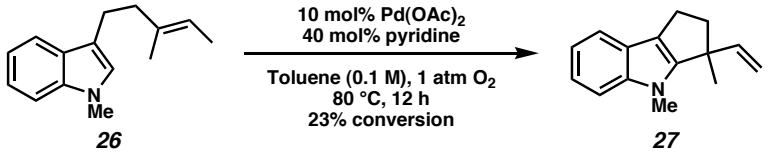


4.3 The Synthesis of Annulated Indoles via Palladium-Catalyzed Oxidative Carbocyclization

4.3.1 Reaction Development

As an initial test of the viability of a catalytic oxidative indole annulation, indole **26** was treated with 10 mol% $Pd(OAc)_2$ and 40 mol% pyridine under 1 atm O_2 in toluene at 80 °C (Scheme 4.3.1).[26] Gratifyingly, oxidative cyclization to annulated indole **27** occurred;[27] the overall reactivity, however, was noticeably sluggish (23% conversion after 12 h) relative to the other oxidative processes studied thus far (i.e., alcohol oxidation[1] and various heterocyclizations[2]). It was hypothesized that the catalyst center was not sufficiently electron-deficient for substrate activation. By increasing the electrophilicity of the catalyst, potentially higher reaction rates could be achieved.

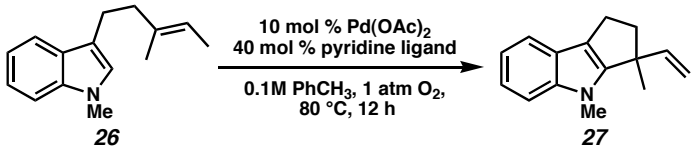
Scheme 4.3.1



To that end, we surveyed a range of electronically differentiated pyridine ligands with $Pd(OAc)_2$ (Table 4.3.1). Interestingly, there was a noticeable correlation between the electronic nature of the ligand (estimated by the measured pK_a of their respective pyridinium ions)[28] and the overall reactivity. More electron-rich pyridine ligands shut down the reaction (entries 1 and 2), while switching to pyridines substituted with electron-withdrawing groups effected an increase in the reactivity, peaking with ethyl nicotinate (entry 5). Further increasing the electron-deficiency, however, was detrimental to the overall reaction (entries 6-9). These ligands are likely unable to sufficiently

coordinate to the palladium center, hampering the catalyst's reactivity and/or palladium(0) reoxidation. Because ethyl nicotinate appeared to strike the appropriate electronic balance for overall reactivity, it was selected as the ligand for further studies.

Table 4.3.1 Examination of electronic effects of the pyridyl ligand.



26 *27*

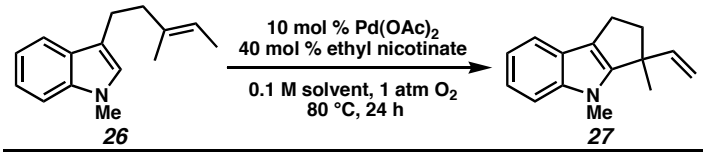
entry	pyridine ligand	pK_a (PyrH$^+$)[a]	conversion (%)[b]
1	4-MeO	6.47	3
2	4-*t*-Bu	5.99	1
3	unsubstituted	5.25	23
4	4-CO_2Et	3.45	52
5	*3-CO_2Et*	*3.35*	*76*
6	3-$COCH_3$	3.18	58
7	3-F	2.97	64
8	3-CN	1.39	55
9	3,5-di-Cl	0.90	22

[a] Reference 28. [b] % conversion measured by GC relative to an internal standard.

With the optimal ligand in hand, other parameters in the oxidative cyclization of indole **26** were investigated. The choice of palladium(II) salt was found to be important; $Pd(OAc)_2$ was more effective than $Pd(TFA)_2$, in contrast to the heterocyclization chemistry.[2] $PdCl_2$ and other palladium(II) halides were completely unreactive. The most significant effects on the reaction outcome were determined by the solvent (Table 4.3.2). Moving from nonpolar aromatic solvents (entries 1-3) to more polar solvents moderately increased the reactivity and overall yield of annulated indole **27**. There was still a noticeable discrepancy, however, between the conversion of **26** and the overall yield of **27**.[29] At this point, the combined yield of **26** and **27** (starting material and product) was observed to decrease in a nonlinear fashion over time. One possible rationalization of this observation is that the product decomposes over the course of the reaction.[30] Interestingly, this problem could be minimized by the addition of AcOH as a cosolvent

(entries 10 and 11). Ultimately, we found that employing a 4:1 mixture of *t*-amyl alcohol and AcOH as the solvent resulted in an 82% isolated yield of annulated indole **27**.

Table 4.3.2 Solvent effects in the indole annulation.



26 *27*

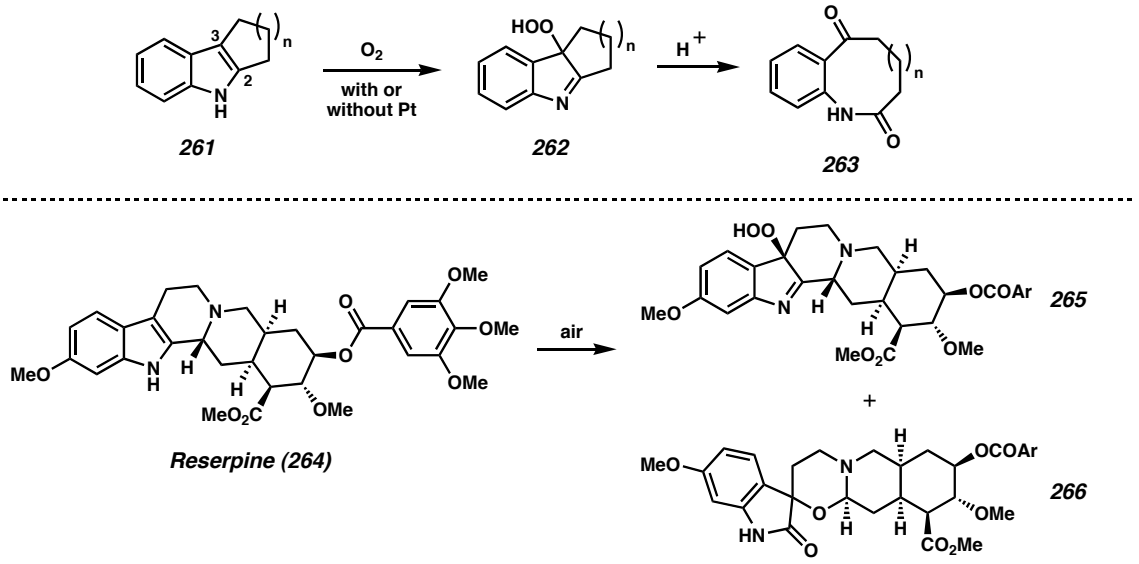
entry	solvent	conversion (%)[a]	% yield[a]
1	toluene	88	33
2	xylenes	88	31
3	chlorobenzene	85	40
4	dioxane	87	42
5	diglyme	99	37
6	butyl acetate	95	49
7	*t*-amyl alcohol	94	53
8	pinacolone	95	58
9	AcOH	86	25
10	pinacolone/AcOH (4:1)	91	76
11	*t*-amyl alcohol/AcOH (4:1)	99	82[b]

[a] % conversion and % yield measured by GC relative to an internal standard. [b] Isolated yield.

4.3.2 Susceptibility of Annulated Indoles to Oxygen

This difficulty with product decomposition was somewhat anticipated considering previous reports on reactions of 2,3-disbustituted indoles with oxygen.[31] In 1951, Witkop described the autoxidation of indoles with fused rings attached to the C-2 and C-3 positions (**261**, Scheme 4.3.2).[32] Under an oxygen atmosphere with or without reduced platinum oxide, the indoles were converted to intermediate peroxides by addition at the C-3 position, which upon workup afford keto lactams (**263**). More recently, the oxidation of reserpine (**264**), which contains an annulated indole core, under an atmosphere of oxygen was investigated by Awang (Scheme 4.3.2).[33] Two products were observed, peroxide **265** and dioxyreserpine (**266**), that arose from reaction with oxygen at ambient temperature.

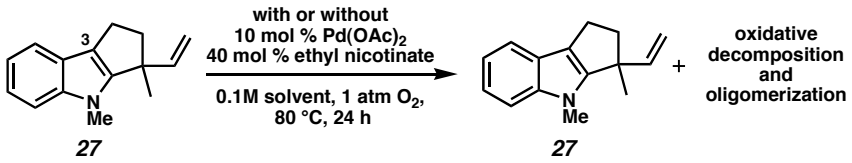
Scheme 4.3.2

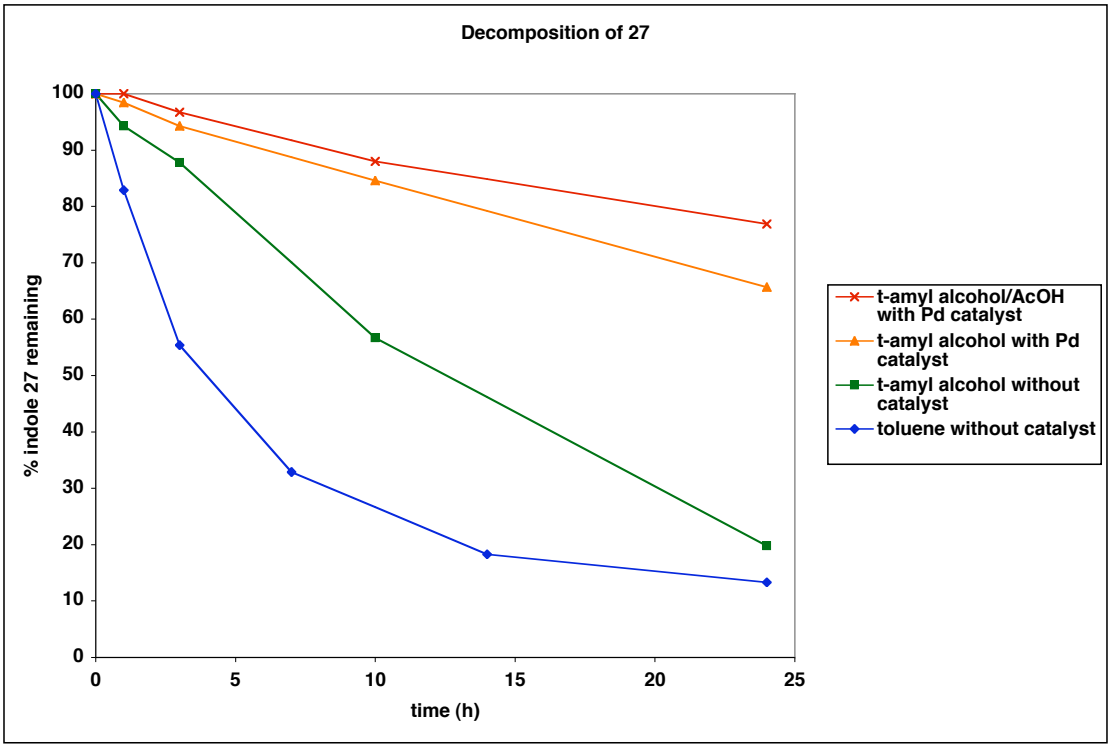


The product decomposition of our oxidative indole cyclization was probed in more detail (Scheme 4.3.1). Annulated indole **27** was subjected to the reaction conditions for 24 h, and the decomposition was monitored by GC analysis relative to an internal standard (tridecane).[34] A slight increase in product stability was observed in *t*-amyl alcohol versus toluene, consistent with our observations of the cyclization reaction. Addition of the catalyst (10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate) had a remarkable impact, limiting product decomposition to approximately 30% over 24 h. The stability was improved further by addition of AcOH as a cosolvent. The reasons behind the beneficial nature of the catalyst and AcOH toward the suppression of oxidative decomposition are currently unclear. One potential explanation is that since oxidative decomposition is initiated by nucleophilic addition of indole into dioxygen, the electrophilic palladium center may act as a competitive inhibitor via palladation at C-3. AcOH could act either as a second competitive inhibitor via association at C-3 or as an

ionizing agent for $L_nPd(OAc)_2$, protonating off an acetate ligand to afford a more reactive cationic palladium(II) center.[35]

Figure 4.3.1 Oxidative decomposition studies of indole **27**.



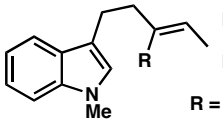
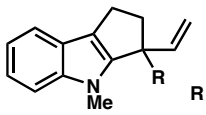
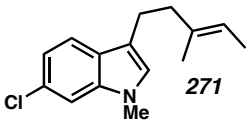
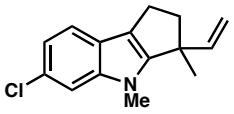
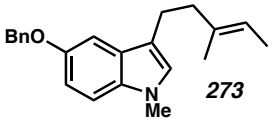
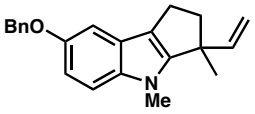
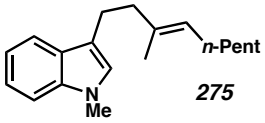
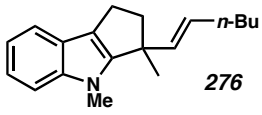
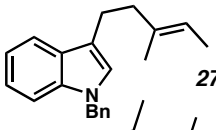
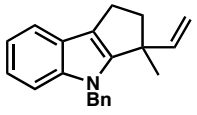
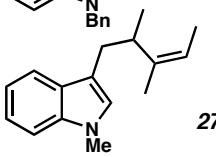
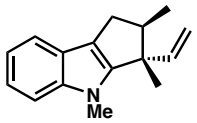
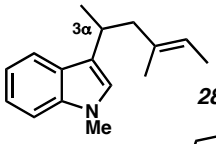
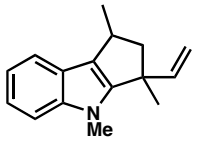
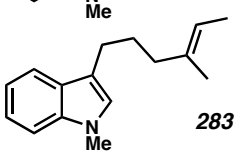
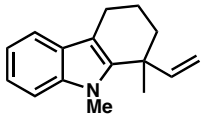
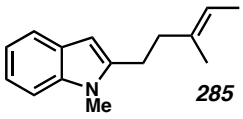
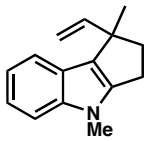
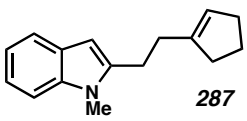
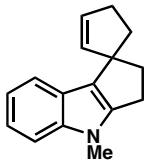
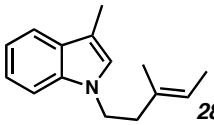
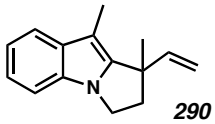


4.3.3 Substrate Scope

With this optimized system now in hand, the substrate scope was investigated. As shown in Table 4.3.3, good to excellent yields can be obtained across a range of substituted indoles. Indoles substituted with electron-withdrawing or electron-donating groups on the arene cyclize efficiently (entries 4 and 5). Substitution on the tether α to the olefin resulted in a diastereoselective cyclization (entry 8), whereas substitution at the

C-3α site imparted no diastereoselectivity (entry 9). Ring sizes of 5 or 6 (entry 10) can be accessed via the oxidative cyclization. The annulation is not limited to bond formation at the C-2 position. The cyclization can proceed from the C-2 to C-3 positions (entries 11 and 12), as well as from N-1 to C-2 (entry 13).[36]

Table 4.3.3 The palladium-catalyzed oxidative indole annulation.[a]

entry	substrate[b]	product	time	% yield[c]
1	 R = Me ***26***	 R = Me ***27***	24 h	82
2	R = Et ***267***	R = Et ***268***	18 h	74
3	R = CH_2OBn ***269***	R = CH_2OBn ***270***	24 h	60
4	 ***271***	 ***272***	32 h	62
5	 ***273***	 ***274***	20 h	73
6	 ***275***	 ***276***	30 h	79[d]
7	 ***277***	 ***278***	48 h	69
8	 ***279***	 ***280***	18 h	76 (6:1 dr)
9	 ***281***	 ***282***	53 h	64 (1:1 dr)
10	 ***283***	 ***284***	39 h	66[e]
11	 ***285***	 ***286***	6 h	73[f]
12	 ***287***	 ***288***	5 h	68[f]
13	 ***289***	 ***290***	18 h	74

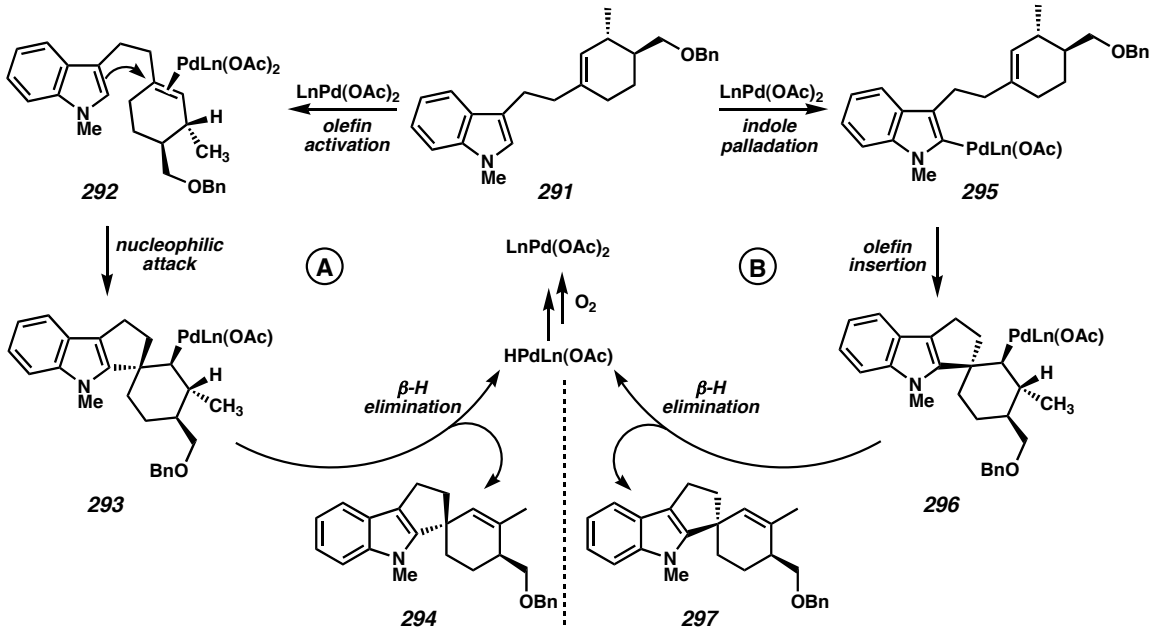
[a] 10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 1 atm O_2, 80 °C, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1). [b] Typically used as a mixture of olefin isomers; see Experimental Section. [c] Isolated yields. [d] Product isolated as a 58:42 mixture of olefin isomers. [e] 0.1 M in pinacolone. [f] 0.1 M in *tert*-amyl alcohol.

4.3.4 Mechanistic Insights

The relative rates of reactivity of the substrates with substitutions on the tethering carbons between the indole nucleus and the olefin (i.e., entries 8 and 9) were particularly interesting; substrate **281** was considerably slower in the cyclization than substrate **279**. This observation pointed toward a mechanism involving initial palladation at C-2, followed by olefin insertion and β-hydride elimination. Branching at the C-3α position (as in substrate **281**) would be expected to sterically interfere with the palladation event, which would cause a decrease in the overall rate. An alternative mechanism involves palladium(II) electrophilic activation of the olefin, intramolecular nucleophilic attack by the indole, and β-hydride elimination akin to the Wacker-type mechanism, which we believed was operative in our heterocyclization studies.[37]

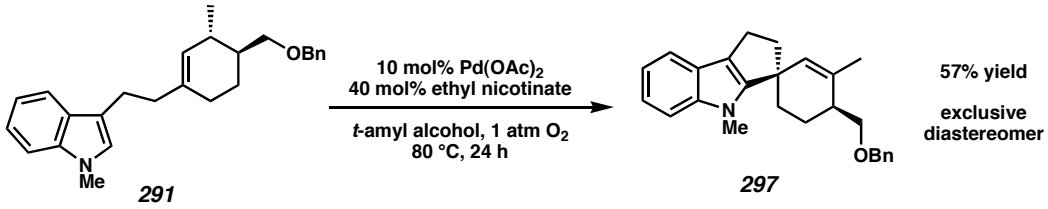
In order to differentiate between these two possible pathways, we designed a cyclization substrate that could act as a mechanistic probe (**291**, Scheme 4.3.3). In pathway A, the cyclization of diastereomerically pure indole **291** proceeds via olefin activation, anti nucleophilic attack, and syn β-hydride elimination to afford annulated indole **294**. The availability of only one β-hydrogen and the general assumption of both an anti nucleophilic attack and a syn β-hydride elimination explain the expected stereochemistry of the product indole. Pathway B proceeds by initial palladation, followed by syn olefin insertion and syn β-hydride elimination. In this case, a syn insertion and elimination are assumed to be operative, as is typical for palladium-catalyzed reactions, ultimately resulting in product indole **297**, which is diastereomerically distinct from **294**.

Scheme 4.3.3



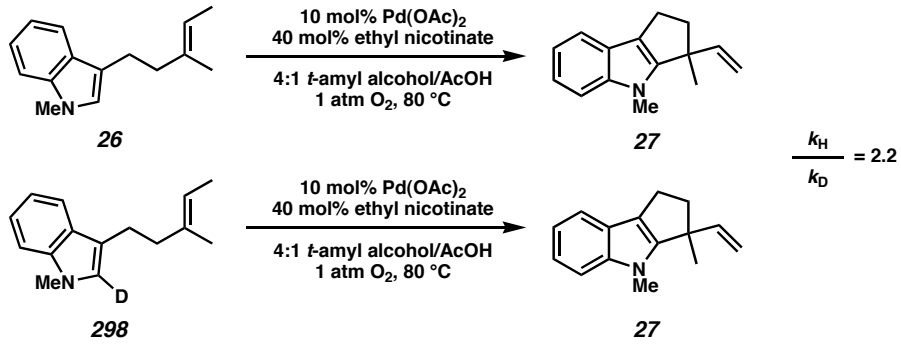
Indole **291** was subjected to the standard indole annulation conditions (10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 1 atm O_2, 80 °C in *t*-amyl alcohol[38]). Annulated indole **297** was thus obtained in 57% yield as a single diastereomer.[39] This result strongly suggested that the reaction was proceeding through initial palladation (net C-H bond functionalization), followed by olefin insertion and β-hydride elimination (pathway B). The mechanism elucidated here is in full agreement with those previously proposed for related reactions.[14a,19] Additionally, this reaction highlights the capacity of this chemistry to set quaternary carbon centers diastereoselectively via a chirality transfer from a tertiary carbon center.

Scheme 4.3.4



To further verify the C-H bond functionalization pathway, the rate of cyclization of indole **26** was compared to that of (C-2)-deuteroindole **298** (Scheme 4.3.5). The rates of consumption of **26** and **298** were measured by GC analysis. The kinetic isotope effect for this cyclization was measured to be 2.2, which is consistent with kinetic isotope effects measured for other palladium(II)-catalyzed reactions involving C-H bond functionalization events.[40] This value also suggests that C-H bond functionalization is a slow step in the catalytic cycle.

Scheme 4.3.5

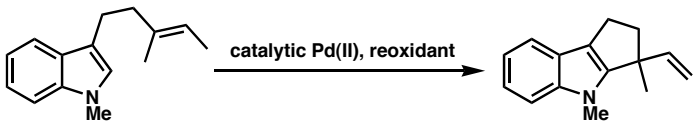


4.3.5 Methodology Comparisons

A direct comparison of the indole annulation method we have developed to other known oxidative palladium(II)-catalyzed C-C bond forming reactions highlights the remarkable efficacy of our system (Table 4.3.4). Indole **26** was subjected to a variety of

previously reported oxidative systems employing different solvent systems and oxidants.[14,15,41] Clearly, the $Pd(OAc)_2$/ethyl nicotinate/O_2/*t*-amyl alcohol/AcOH conditions are vastly superior at catalyzing this annulation. The desired product was observed in only three other cases, with the highest yield reaching just 13%. Even the conditions that were highly successful for the indole oxidative coupling reported by Fujiwara[15] were ineffective for this transformation (entry 8). The oxidative system described herein holds immense potential for other oxidative C-C bond forming reactions, where previously developed conditions may be too harsh or simply ineffective.

Table 4.3.4 Comparison of methods for the oxidative annulation of **26**.



26 ***27***

entry	conditions[a]	ref	% yield[b]
1	$Pd(OAc)_2$, AgOAc, AcOH, air, 110 °C	14a	4
2	$Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, air, 110 °C	14a	0
3	$Pd(OAc)_2$, $K_2S_2O_8$, AcOH, air, 110 °C	14a	0
4	$Pd(OAc)_2$, $NaNO_2$, AcOH, air, 110 °C	14a	0
5	$Pd(OAc)_2$, $Cu(OAc)_2$, Dioxane/AcOH (4:1), O_2, 100 °C	40a	13
6	$Pd(OAc)_2$, benzoquinone, $TsOH{\cdot}H_2O$, Toluene/AcOH (2:1), O_2, 23 °C	40b	0
7	$Pd(OAc)_2$, $H_6PMo_9V_3O_{40}$, acetylacetonate, NaOAc AcOH, O_2, 90 °C	40c	0
8	$Pd(OAc)_2$, cat. benzoquinone, TBHP $AcOH/Ac_2O$ (4:1), 50 °C	15	5
9	$Pd(OAc)_2$, ethyl nicotinate, t-amyl alcohol/AcOH (4:1), O_2, 80 °C		82

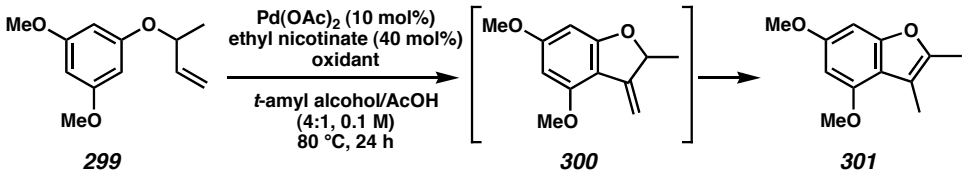
[a] For details, see Experimental Section. [b] % yield measured by GC relative to an internal standard.

4.4 The Synthesis of Benzofurans and Dihydrobenzofurans via Oxidative Carbocyclizations

In hopes of further developing the oxidative C-H bond functionalization systems, Dr. Haiming Zhang, a postdoctoral scholar in our laboratory, extended the chemistry toward the synthesis of benzofurans and dihydrobenzofurans. Discussed herein is a brief account of his work on this project.[8b]

Aryl allyl ether **299** was subjected to the optimized conditions from the indole annulation chemistry (10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 4:1 *t*-amyl alcohol/AcOH, 1 atm O_2, 80 °C) to provide benzofuran **301** in 56% yield (Table 4.4.1, entry 1). This reaction presumably proceeds via an initial C-H bond functionalization, followed by 5-exo cyclization and β-hydride elimination to afford intermediate **300**. The intermediate then isomerizes to the more thermodynamically stable aromatic compound **301**.[42] With this promising result, a variety of oxidants were evaluated in this oxidation system. Although moderate yields of **301** were obtained with a number of oxidants, oxygen and benzoquinone provided the highest yields (entries 1 and 2). Benzoquinone led to the greatest yield of **301** and was therefore used in subsequent optimization studies.

Table 4.4.1 Oxidant screen for the synthesis of benzofuran **301**.



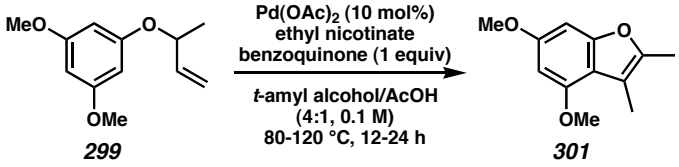
299 ***300*** ***301***

entry	oxidant (1 equiv)	% yield[a]	entry	oxidant (1 equiv)	% yield[a]
1	O_2 (1 atm)	56	5	$Tl(O_2CCF_3)_3$	<10
2	benzoquinone	62	6	$K_2S_2O_8$	30
3	$Cu(OAc)_2$	31	7	$H_2NC(S)NH_2$	<10
4	$Ag(OAc)_2$	29	8	$PhCO_3$-*t*-Bu	42

[a] % yield measured by GC relative to an internal standard.

Other parameters were then examined in the oxidative cyclization of aryl allyl ether **299** (Table 4.4.2). The ratio of ligand:palladium was found to be important for this reaction, a 2:1 system being optimal. This is likely reflective of a balance between the sufficient ligation of the palladium center for Pd(0) reoxidation and the suppression of competitive binding caused by the presence of excess ligand. Further optimization studies revealed that adding 20 mol% NaOAc and increasing the temperature to 100 °C were both beneficial to the overall transformation, providing the highest yield of benzofuran **301** (77% isolated yield, entry 7).

Table 4.4.2 Optimization studies for the synthesis of benzofuran **301**.

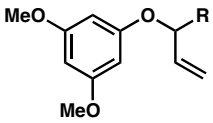
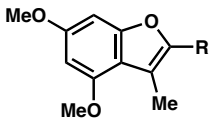
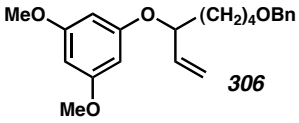
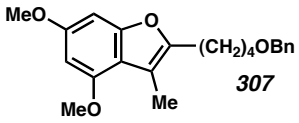
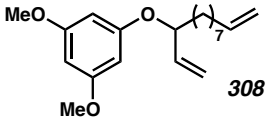
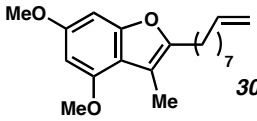
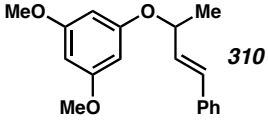
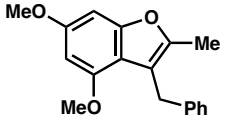
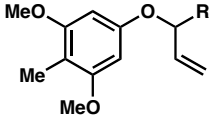
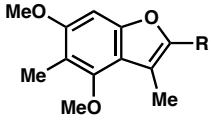
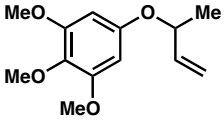
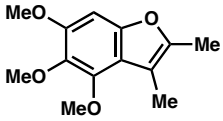
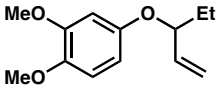
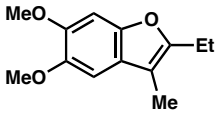
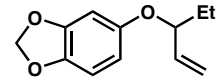
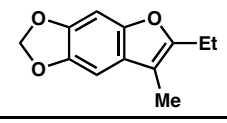


entry	ethyl nicotinate	additive	temp (°C)	time (h)	% yield[a]
1	40 mol%	–	80	24	62
2	20 mol%	–	80	24	66
3	10 mol%	–	80	24	59
4	0 mol%	–	80	24	55
5	20 mol%	NaOAc (1 equiv)	80	24	70
6	20 mol%	NaOAc (20 mol %)	80	24	74
7	20 mol%	NaOAc (20 mol %)	100	12	80 (77)[b]
8	20 mol%	NaOAc (20 mol %)	120	12	67

[a] % yield measured by GC relative to an internal standard.
[b] Isolated yield in parentheses.

The generality of the palladium-catalyzed benzofuran synthesis was then explored. As shown in Table 4.4.3, this process works for a variety of allyl aryl ethers with various substitution patterns, all resulting in good yields. This reaction is currently limited to electron-rich aryl groups; the palladation event requires a sufficiently nucleophilic arene in order to occur. The aryl subunit, however, tolerates various alkyl and alkoxy substitution patterns within the electronic requirements. The allyl moiety can also accommodate several substituents (aryl, alkyl, alkoxy) at both the proximal and distal positions.

Table 4.4.3 The palladium(II)-catalyzed oxidative benzofuran synthesis.[a]

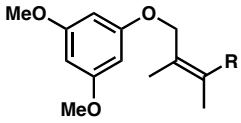
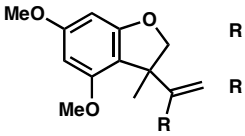
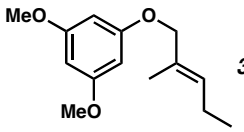
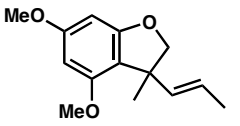
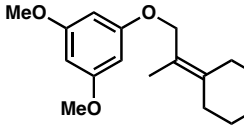
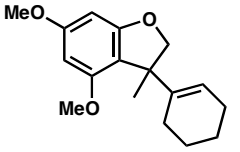
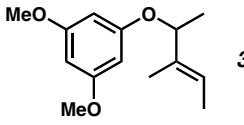
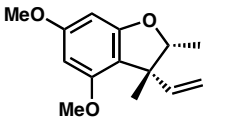
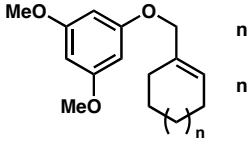
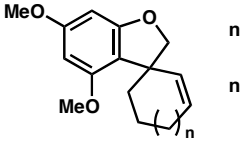
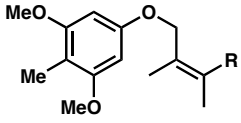
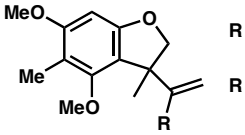
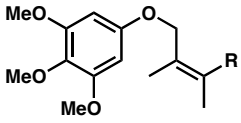
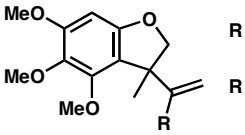
entry	substrate	product	time (h)	% yield[b]
1	 R = Me ***299***	 R = Me ***301***	12	77
2	R = Et ***302***	R = Et ***303***	12	74
3	R = *n*-C_5H_{11} ***304***	R = *n*-C_5H_{11} ***305***	13	72
4	 ***306***	 ***307***	12	62
5	 ***308***	 ***309***	14	54
6	 ***310***	 ***311***	12	61
7	 R = Me ***312***	 R = Me ***313***	14	75
8	R = Et ***314***	R = Et ***315***	12	79
9	 ***316***	 ***317***	12	61
10	 ***318***	 ***319***	16	56[c]
11	 ***320***	 ***321***	16	52[c]

[a] 10 mol% $Pd(OAc)_2$, 20 mol% ethyl nicotinate, 20 mol% NaOAc, 1 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C. [b] Isolated yield. [c] Produced as a single regioisomer.

This methodology was then extended to aryl allyl ethers in which the allyl group possessed tri- and tetrasubstituted olefins. The dihydrobenzofuran products of these reactions can be obtained in good to excellent yields (Table 4.4.4). Dihydrobenzofurans are produced in these reactions because the substitution patterns lack hydrogens at the point of C-C bond formation that could eliminate to intermediates similar to **300** (*vide*

supra, Table 4.4.1). An array of aryl and allyl substitution patterns are tolerated in this reaction.

Table 4.4.4 The palladium(II)-catalyzed oxidative dihydrobenzofuran synthesis.[a]

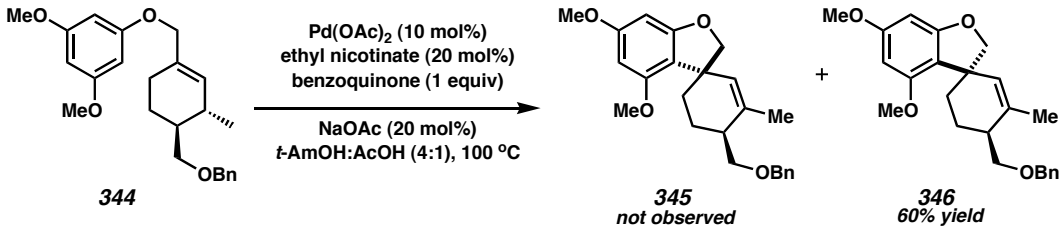
entry	substrate		product		time (h)	% yield[b]
1		R = H ***322***		R = H ***323***	16	74
2[c]		R = Me ***324***		R = Me ***325***	12	71
3		***326***		***327***	30	58[d]
4		***328***		***329***	28	55
5		***330***		***331***	15	74[e]
6		n = 1 ***332***		n = 1 ***333***	24	80
7		n = 0 ***334***		n = 0 ***335***	18	78
8		R = H ***336***		R = H ***337***	15	50
9		R = Me ***338***		R = Me ***339***	15	63
10		R = H ***340***		R = H ***341***	15	60
11		R = Me ***342***		R = Me ***343***	15	66

[a] 10 mol% $Pd(OAc)_2$, 20 mol% ethyl nicotinate, 20 mol% NaOAc, 1 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C. [b] Isolated yield. [c] Performed with 5 mol% $Pd(OAc)_2$ and 10 mol% ethyl nicotinate. [d] An inseparable mixture of roughly 66% product (*E*/*Z* = 3:1) and 10% starting material was isolated after 18 h. This mixture was subjected to another reaction with 5 mol% $Pd(OAc)_2$, 10 mol% ethyl nicotinate, 20 mol% NaOAc, and 50 mol% benzoquinone for 12 h, after which only the *E* isomer was observed. The yield presented is the overall yield of isolated product. [e] A 2.3:1 mixture of diastereomers was isolated with the major isomer shown.

Analogous to the indole annulation studies (*vide supra*), aryl allyl ether **344** was subjected to the cyclization conditions as a mechanistic probe (Scheme 4.4.1). As in the

indole case, this experiment differentiates between an olefin activation/nucleophilic attack pathway (to produce **345)** and an arene palladation/olefin insertion pathway (to produce **346**). In the event, the product dihydrobenzofuran (**346**) was isolated as a single diastereomer.[43] This experiment strongly suggests that the palladation pathway (a net C-H bond functionalization) is operative, which correlates with the result from the indole study.

Scheme 4.4.1

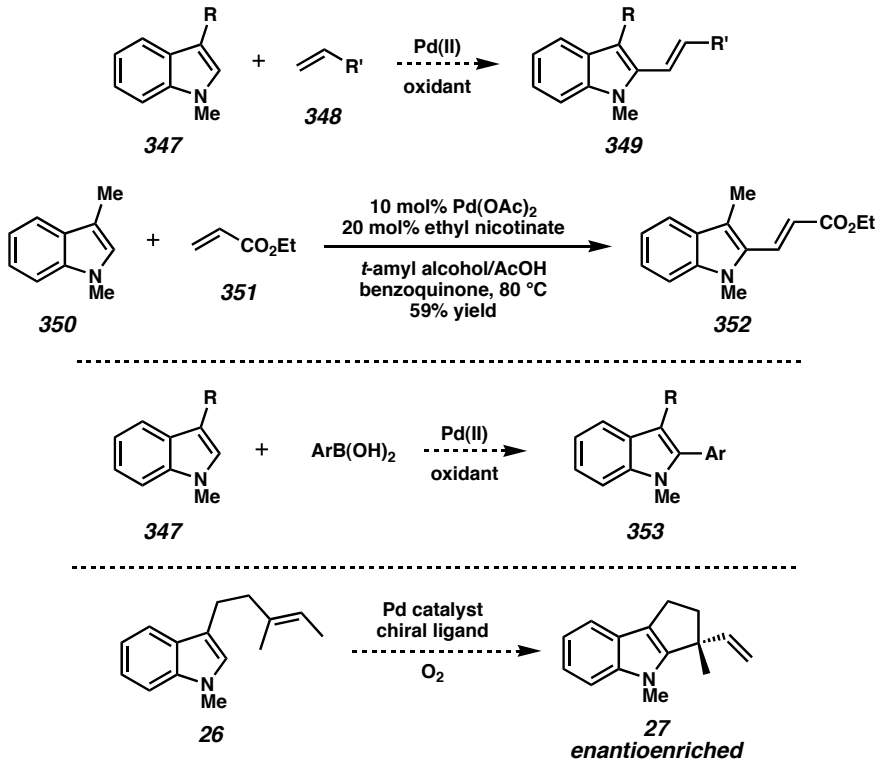


4.5 Future Directions

There are a number of future directions for this chemistry. Currently, only intramolecular oxidative reactions have been studied in detail. Intermolecular examples that initiate with a similar C-H bond functionalization followed by olefin insertion and β-hydride elimination can be envisioned (Scheme 4.5.1). This transformation is similar to the lone indole example reported recently by Fujiwara.[15,44] As an initial test, 1,3-dimethylindole was oxidatively coupled to ethyl acrylate under conditions similar to those utilized in the benzofuran chemistry.[45] This promising lead establishes that intermolecular examples are indeed possible. The C-H bond functionalization event could also be followed by transmetallation and reductive elimination processes (e.g., **347** → **353**), analogous to cross-couplings such as Suzuki and Stille reactions. The research described herein opens the possibility of extending these annulations to asymmetric

variants. We have demonstrated that the Pd/pyridine system can be readily modified to enantioselective versions in other reaction manifolds.[1,2] Perhaps the same concept can be applied to the carbocyclization chemistry described herein (e.g., **26** → **27**) to set quaternary centers enantioselectively.[46]

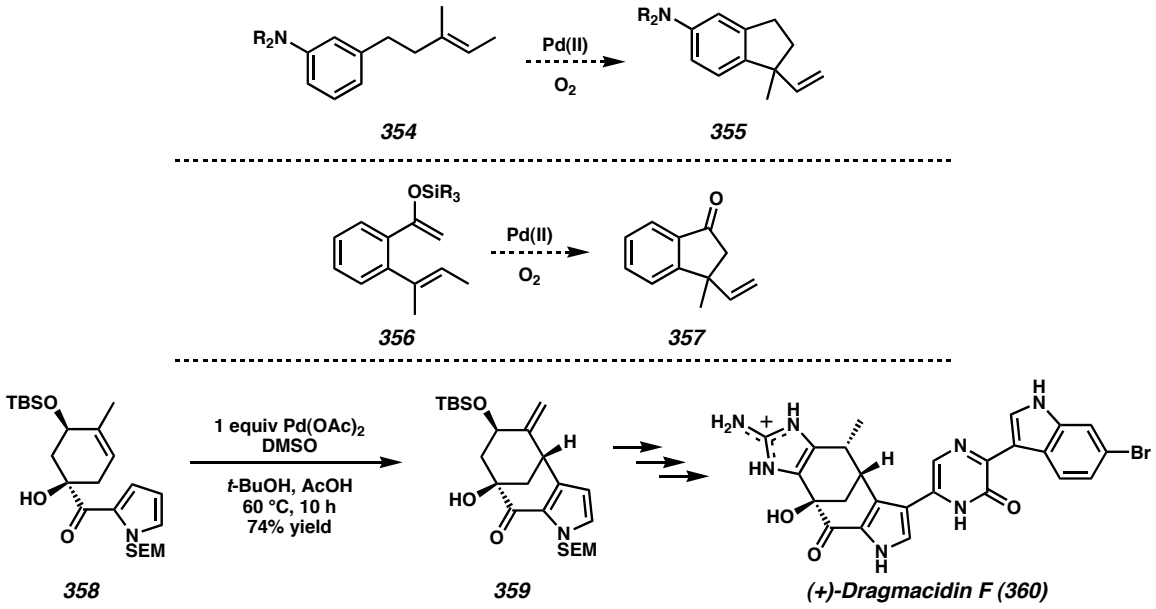
Scheme 4.5.1



Another interesting extension would be to apply this chemistry to other electron-rich systems (Scheme 4.5.2). Currently, we have only studied indoles and oxygenated aryl groups as the carbon nucleophile in these cyclizations. These oxidative systems could potentially be extended to aniline derivatives (e.g., **354**) or silyl enol ethers (e.g., **356**).[47] One example, discovered by Neil Garg and Daniel Caspi in our laboratories, has been utilized in the total synthesis of dragmacidin F (**360**).[48] In one of the key transformations of the synthesis, acyl pyrrole **358** was oxidatively cyclized to tricycle **359**

using stoichiometric palladium(II) conditions.[49] Substrate variation or parameter optimization could lead to the discovery of catalytic variants more similar to our cyclization studies. The carbocyclization studies outlined above have clear and immediate impacts in total synthesis and methodology.

Scheme 4.5.2



4.6 Conclusion

We have developed a remarkably mild oxidative system for C-C bond forming reactions that involves a C-H bond functionalization event. Annulated indoles, benzofurans, and dihydrobenzofurans can all be accessed through this chemistry, which could have widespread implications in total synthesis. In the indole carbocyclizations, molecular oxygen is the sole stoichiometric oxidant, the inexpensive and abundant reagent affording only water as a byproduct. These cyclizations are also the first examples to demonstrate the use of electronically tuned pyridine ligands in the standard

Pd/pyridine system. This electronic tuning has led to the discovery of unique reactivities that were unavailable under the original conditions.

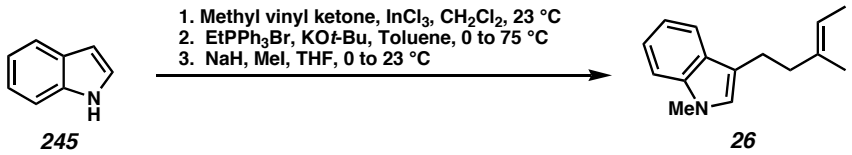
C-H bond functionalization continues to be an active and engaging area of research. Outlined herein is an oxidative catalytic approach to C-C bond forming reactions that involves an initial C-H bond functionalization step, followed by an intramolecular cyclization onto an unactivated olefin. This is directly analogous to the corresponding intramolecular Heck reaction, but does not involve the prior halogenation necessary for the palladium(0) process. Furthermore, the oxidative carbocyclization can be considered orthogonal to the Heck reaction, as the electron-rich aromatic systems utilized in this study can be employed directly. Generally, selectively halogenated derivatives of these types of arenes can be difficult to access; additionally, electron-rich aryl halides are typically poor reactants toward oxidative addition to palladium(0) species. Both of these complicating factors are circumvented by the oxidative cyclization chemistry. The transformations described herein provide a promising future area for the development of powerful catalytic dehydrogenative carbon-carbon bond forming reactions.

4.7 Experimental Section for the Oxidative Annulation of Indoles

4.7.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical GC was carried out using a DB-1701 column (30.0 m x 0.25 mm) from Agilent Technologies. ^{1}H spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C spectra were recorded on a Varian Mercury 500 (at 125 MHz) or on a Varian Mercury 300 (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. Unless otherwise noted, compounds that are mixtures of *E* and *Z* olefin isomers are reported as the mixture as seen by ^{1}H NMR. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. $Pd(OAc)_2$ was purchased from Strem Chemicals, Inc., Newburyport, MA. Titanium(III) chloride solution in 3% HCl was purchased from Alfa Aesar, Ward Hill, MA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

4.7.2 Preparative Procedures

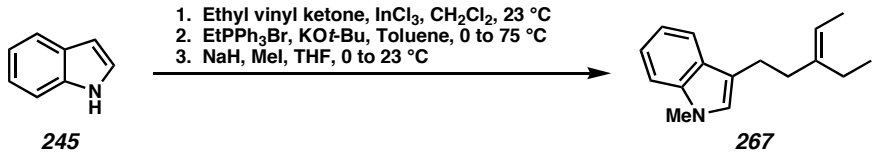


245 *26*

Indole 26. Indium catalyzed conjugate additions of indoles were done according to the procedure of Yadav et al.[50] To a solution of indole (5.00 g, 42.7 mmol) in 85.4 mL CH_2Cl_2 at 23 °C was added methyl vinyl ketone (3.55 mL, 42.7 mmol) and $InCl_3$ (944 mg, 4.27 mmol). The reaction mixture was stirred at 23 °C for 4 h, quenched with water (160 mL), and extracted with CH_2Cl_2 (2 x 200 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to a brown solid. The solid was dissolved in CH_2Cl_2 and passed through a plug of SiO_2 (5 x 5 cm, 4:1 CH_2Cl_2/hexanes eluent). The filtrate was evaporated to provide the ketone[50] (6.49 g, 81% yield, R_F = 0.22 in 100% CH_2Cl_2) as a white solid.

To a suspension of potassium *tert*-butoxide (7.50 g, 66.8 mmol) in toluene (267 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (24.8 g, 66.8 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the indolyl ketone (5.00 g, 26.7 mmol) was added as a solid, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (250 mL, 1:1), and extracted with EtOAc (2 x 250 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin[51] (4.31 g, 81% yield, R_F = 0.67 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (4.31 g, 21.6 mmol) in THF (86.4 mL) at 0 °C was added NaH (1.73 g, 60% dispersion in mineral oil, 43.2 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (2.02 mL, 32.4 mmol), and allowed to warm to 23 °C. After 30 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (100 mL), and extracted with ether (2 x 250 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **26** (3.67 g, 80% yield, R_F = 0.48 in 9:1 hexanes/EtOAc, 59:41 mixture of olefin isomers) as a clear oil. **Indole 26**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.33 (app.t, *J* = 7.7 Hz, 1H), 7.33 (app.t, *J* = 7.7 Hz, 1H), 7.31-7.25 (m, 1H), 7.31-7.25 (m, 1H), 7.20-7.13 (comp m, 1H), 7.20-7.13 (comp m, 1H), 6.90 (s, 1H), 6.88 (s, 1H), 5.37 (app.q, *J* = 6.6 Hz, 1H), 5.33 (app.q, *J* = 6.6 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.90 (t, *J* = 8.8 Hz, 2H), 2.88 (t, *J* = 8.5 Hz, 2H), 2.52-2.42 (comp m, 2H), 2.52-2.42 (comp m, 2H), 1.84 (s, 3H), 1.77 (s, 3H), 1.67 (d, *J* = 6.6 Hz, 3H), 1.63 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 136.3, 136.2, 128.1, 126.1, 121.6, 119.5, 119.2, 118.7, 115.6, 109.3, 40.7, 32.8, 32.7, 24.2, 23.6, 16.0, 13.6, 13.5; IR (film) 2916, 1473, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{19}N]^+$: 213.1517, found 213.1514.



245 *267*

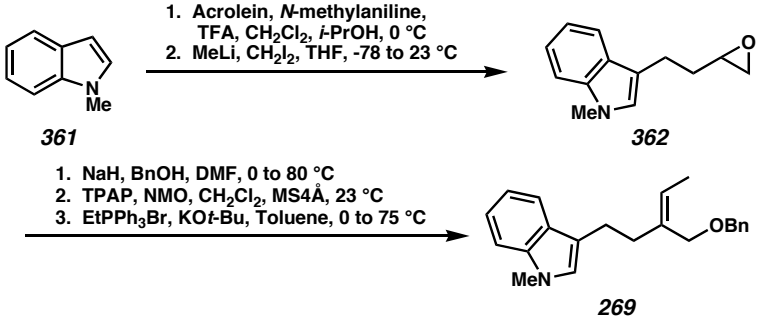
Indole 267. Indium-catalyzed conjugate additions of indoles were done according to the procedure of Yadav et al.[50] To a solution of indole (1.61 g, 13.7 mmol) in CH_2Cl_2 (27.4

mL) at 23 °C was added ethyl vinyl ketone (1.36 mL, 13.7 mmol) and $InCl_3$ (303 mg, 1.37 mmol). The reaction mixture was stirred at 23 °C for 4 h, quenched with water (50 mL), and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was purified by flash chromatography (2:1 to 4:1 CH_2Cl_2/hexanes eluent) to provide the ketone[52] (2.25 g, 82% yield, R_F = 0.38 in CH_2Cl_2) as a white solid.

To a suspension of potassium *tert*-butoxide (1.39 g, 12.4 mmol) in toluene (49.7 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (4.60 g, 12.4 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (1.00 g, 4.97 mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin (990 mg, 93% yield, R_F = 0.32 in 9:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (990 mg, 4.64 mmol) in THF (18.6 mL) at 0 °C was added NaH (297 mg, 60% dispersion in mineral oil, 7.42 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (375 μl, 6.03 mmol), and allowed to warm to 23 °C. After 30 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (50 mL), and extracted with ether (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was

purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **267** (830 mg, 79% yield, R_F = 0.69 in 4:1 hexanes/EtOAc, 56:44 mixture of olefin isomers) as a clear oil. **Indole 267**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.25 (m, 1H), 7.25 (m, 1H), 7.17-7.11 (comp m, 1H), 7.17-7.11 (comp m, 1H), 6.89 (s, 1H), 6.87 (s, 1H), 5.33 (app.q, *J* = 6.6 Hz, 1H), 5.31 (app.q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.90-2.80 (comp m, 2H), 2.90-2.80 (comp m, 2H), 2.50-2.40 (comp m, 2H), 2.50-2.40 (comp m, 2H), 2.22-2.11 (comp m, 2H), 2.22-2.11 (comp m, 2H), 1.66 (app.d, *J* = 6.6 Hz, 3H), 1.65 (app.d, *J* = 6.6 Hz, 3H), 1.09 (app.t, *J* = 7.7 Hz, 3H), 1.06 (app.t, *J* = 7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 142.0, 137.2, 128.0, 126.1, 121.6, 119.2, 118.7, 118.1, 117.8, 115.7, 109.3, 37.7, 32.7, 31.3, 30.0, 24.4, 24.1, 23.2, 13.4, 13.2, 13.1; IR (film) 2964, 2930, 1472, 736 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1678.



Indole 269. To a solution of acrolein (4.62 mL, 70.5 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (179 μl, 1.65 mmol) and trifluoroacetic acid (127 μl, 1.65 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h, then

filtered through a pad of silica gel (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (6:1 hexanes/EtOAc eluent) provided the aldehyde[53] (3.54 g, 80% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a yellow oil.

The epoxide was synthesized according to a modified procedure of Cainelli et al.[54] To a solution of the aldehyde (500 μl, 2.91 mmol) and diiodomethane (422 μl, 5.24 mmol) in THF (11.6 mL) at –78 °C was added methyllithium (3.28 mL, 1.6 M in Et_2O, 5.24 mmol) dropwise over 3 min. The reaction was stirred for 30 min at –78 °C and 2 h at 23 °C. It was then cooled to 0 °C and quenched by slow addition of saturated NH_4Cl (40 mL). Et_2O (50 mL) was added, the phases separated, and the aqueous layer extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (5:1 hexanes/EtOAc eluent) afforded epoxide **362** (314 mg, 54% yield, R_F = 0.54 in 2:1 hexanes/EtOAc) as a yellow oil.

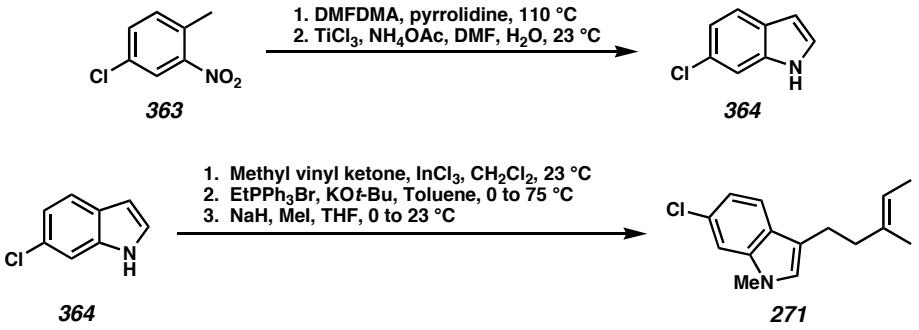
To a solution of benzyl alcohol (475 μl, 4.59 mmol) in DMF (8.5 mL) at 0 °C was added NaH (184 mg, 60% dispersion in mineral oil, 4.59 mmol). The solution was stirred at 0 °C for 10 min and 23 °C for 1 h. The resulting solution of sodium benzyloxide was added to a solution of epoxide **362** (308 mg, 1.53 mmol) in DMF (2.13 mL) at 0 °C. The reaction mixture was then heated to 80 °C and stirred 3 h. The reaction was cooled to 0 °C and quenched with saturated NH_4Cl (50 mL). Et_2O (75 mL) was added, the phases separated, and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to an oil. Purification

of the residue by flash chromatography (1:1 hexanes/Et_2O eluent) afforded the alcohol (304 mg, 64% yield, R_F = 0.30 in 2:1 hexanes/EtOAc) as a yellow oil.

To a solution of the alcohol (304 mg, 0.981 mmol) in CH_2Cl_2 (1.96 mL) at 23 °C was added 4Å molecular sieves (491 mg, 500 mg/mmol substrate), then NMO (172 mg, 1.47 mmol). The suspension was stirred for 15 min, at which point TPAP (17.2 mg, 0.0491 mmol) was added. After stirring 15 min, the reaction mixture was filtered through a pad of silica gel (2 x 7 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. Purification of the oil by flash chromatography (4:1 hexanes/EtOAc eluent) afforded α-benzyloxyketone (265 mg, 86% yield, R_F = 0.50 in 2:1 hexanes/EtOAc) as a clear oil.

To a suspension of potassium *tert*-butoxide (230 mg, 2.05 mmol) in toluene (8 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (761 mg, 2.05 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, a solution of the ketone (294 mg, 0.956 mmol) in toluene (1.56 mL) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (30 mL, 1:1), and extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (2:1 hexanes/CH_2Cl_2 eluent) to provide indole **269** (243 mg, 80% yield, R_F = 0.48 in 4:1 hexanes/EtOAc, 88:12 mixture of olefin isomers) as a clear oil. **Indole 269**: (Major isomer only) ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 1H), 7.40-7.26 (comp m, 6H), 7.22 (app.t, *J* = 7.4 Hz, 1H), 7.09 (app.t, *J* = 7.4 Hz, 1H), 6.83 (s, 1H), 5.58 (q, *J* = 6.8 Hz, 1H), 4.52 (s, 2H), 4.14 (s, 2H), 3.73 (s, 3H), 2.89 (t, *J* = 8.1

Hz, 2H), 2.53 (t, J = 8.1 Hz, 2H), 1.68 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 137.2, 136.9, 128.6, 128.1, 128.0, 127.7, 126.2, 124.1, 121.6, 119.3, 118.7, 115.4, 109.3, 72.2, 67.2, 36.5, 32.7, 24.3, 13.6; IR (film) 1472, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{25}NO]^+$: 319.1936, found 319.1938.



Indole 271. A solution of 4-chloro-2-nitrotoluene (1.00 g, 5.83 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (2.32 mL, 17.5 mmol) and pyrrolidine (1.46 mL, 17.5 mmol) was heated to 110 °C for 1 h. The dark red mixture was cooled to 23 °C and carried on without isolation.

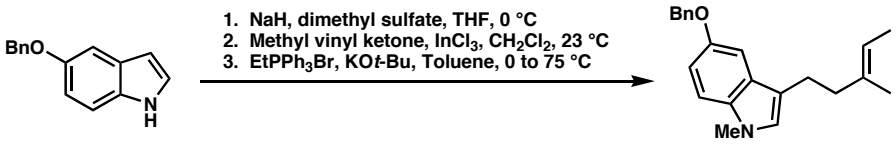
The red mixture was dissolved in DMF (58.3 mL), and to the solution was added NH_4OAc (25 mL, 4.0 M in water) followed by dropwise addition of $TiCl_3$ (21.1 mL, 20% w/v in 3% HCl, 27.4 mmol) over 15 minutes. The temperature was kept at 23 °C by an external water bath. After the addition was complete, the reaction was quenched with 1.0 M NaOH (300 mL) and extracted with ether (5 x 250 mL). The organic layers were combined, washed with water, passed through a plug of SiO_2 (5 x 8 cm, Et_2O eluent), dried over $MgSO_4$, and evaporated to an oil. Purification of the residue by flash chromatography (5:1 hexanes/EtOAc eluent) provided 6-chloroindole[55] (400 mg, 45% yield over 2 steps, R_F = 0.46 in 4:1 hexanes/EtOAc) as a brown solid.

To a solution of 6-chloroindole (400 mg, 2.64 mmol) in CH_2Cl_2 (5.28 mL) at 23 °C was added methyl vinyl ketone (220 μl, 2.64 mmol) and $InCl_3$ (58.4 mg, 0.264 mmol). The reaction mixture was stirred at 23 °C for 2 h, quenched with water (30 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to a brown solid. Purification of the residue by flash chromatography (4:1 CH_2Cl_2/hexanes eluent) provided the ketone (309 mg, 53% yield, R_F = 0.33 in 2:1 hexanes/EtOAc) as a yellow solid.

To a suspension of potassium *tert*-butoxide (230 mg, 2.05 mmol) in toluene (8.21 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (761 mg, 2.05 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (182 mg, 0.821 mmol) was added, and the solution was heated to 75 °C. After stirring for 4 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (20 mL, 1:1), and extracted with EtOAc (2 x 35 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin (128 mg, 67% yield, R_F = 0.50 in 4:! hexanes/EtOAc) as a clear oil.

To a solution of the olefin (74.0 mg, 0.317 mmol) in THF (1.27 mL) at 0 °C was added NaH (25.4 mg, 60% dispersion in mineral oil, 0.634 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (29.6 μl, 0.476 mmol), and allowed to warm to 23 °C. After 30 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (20 mL), and extracted with ether (2 x 30 mL). The organic layers were combined,

washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **271** (70.3 mg, 90% yield, R_F = 0.47 in 9:1 hexanes/EtOAc, 57:43 mixture of olefin isomers) as a clear oil. **Indole 271**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.27 (s, 1H), 7.26 (s, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 6.81 (s, 1H), 5.29 (app.q, *J* = 6.6 Hz, 1H), 5.26 (app.q, *J* = 6.6 Hz, 1H), 3.70 (s, 3H), 3.70 (s, 3H), 2.80 (t, *J* = 8.2 Hz, 2H), 2.78 (t, *J* = 8.2 Hz, 2H), 2.42-2.32 (comp m, 2H), 2.42-2.32 (comp m, 2H), 1.76 (s, 3H), 1.69 (s, 3H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.53 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 136.0, 135.9, 127.7, 126.8, 120.1, 120.0, 119.7, 119.4, 118.9, 115.8, 109.3, 40.6, 32.8, 32.6, 24.0, 23.6, 23.5, 16.0, 13.6, 13.5; IR (film) 2917, 1477, 799 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{18}NCl]^+$: 247.1128, found 247.1123.



365 *273*

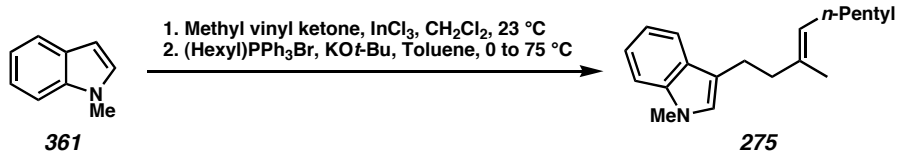
Indole 273. To a solution of 5-benzyloxyindole (500 mg, 2.24 mmol) in THF (8.96 mL) at 0 °C was added NaH (179 mg, 60% dispersion in mineral oil, 4.48 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and at 23 °C for 1 h. The mixture was then cooled to 0 °C and treated with dimethyl sulfate (320 μl, 3.36 mmol). After 30 min, the reaction mixture was quenched with saturated NH_4Cl (40 mL) and extracted with Et_2O (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by flash

chromatography (5:1 hexanes/EtOAc eluent) to provide the methyl indole[56] (493 mg, 93% yield, R_F = 0.49 in 4:1 hexanes/EtOAc) as a white solid.

To a solution of 5-benzyloxy-*N*-methyl indole (493 mg, 2.08 mmol) in CH_2Cl_2 (4.16 mL) at 23 °C was added methyl vinyl ketone (173 µl, 2.08 mmol) and $InCl_3$ (46.0 mg, 0.208 mmol). The reaction mixture was stirred at 23 °C for 2.5 h, quenched with water (25 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide the ketone (450 mg, 70% yield, R_F = 0.42 in 2:1 hexanes/EtOAc) as a white solid.

To a suspension of potassium *tert*-butoxide (328 mg, 2.92 mmol) in toluene (14.6 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (1.08 g, 2.92 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (450 mg, 1.46 mmol) was added, and the solution was heated to 75 °C. After stirring for 4 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (3:1 hexanes/CH_2Cl_2 eluent) to provide indole **273** (418 mg, 90% yield, R_F = 0.64 in 4:1 hexanes/EtOAc, 59:41 mixture of olefin isomers) as a clear oil. **Indole 273**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (app.d, *J* = 7.7 Hz, 2H), 7.51 (app.d, 7.7 Hz, 2H), 7.43-7.31 (comp m, 3H), 7.43-7.31 (comp m, 3H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 5.0 Hz, 1H), 7.15 (d, *J* = 5.5 Hz, 1H), 7.00 (s, 1H), 6.97 (s, 1H), 6.85 (s, 1H), 6.82 (s, 1H), 5.32 (app.q, *J* = 6.6 Hz, 1H), 5.27 (app.q, *J* = 6.6 Hz, 1H), 5.14 (s, 2H), 5.14 (s, 2H), 3.73

(s, 3H), 3.72 (s, 3H), 2.83-2.75 (comp m, 2H), 2.83-2.75 (comp m, 2H), 2.44-2.34 (comp m, 2H), 2.44-2.34 (comp m, 2H), 1.79 (s, 3H), 1.72 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H), 1.57 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 138.1, 136.3, 136.2, 132.9, 128.7, 128.4, 127.9, 127.8, 126.8, 119.5, 118.7, 115.1, 112.5, 110.0, 103.2, 103.1, 71.4, 40.6, 32.9, 32.6, 24.2, 23.7, 16.0, 13.6, 13.5; IR (film) 1489, 1208 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{25}NO]^+$: 319.1936, found 319.1947.

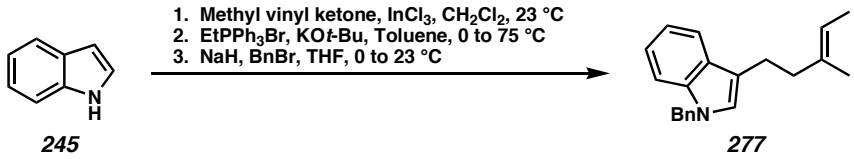


361 *275*

Indole 275. To a solution of 1-methylindole (1.00 mL, 7.82 mmol) in CH_2Cl_2 (15.6 mL) at 23 °C was added methyl vinyl ketone (651 μl, 7.82 mmol) and $InCl_3$ (173 mg, 0.782 mmol). The reaction mixture was stirred at 23 °C for 2.5 h, quenched with water (30 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was purified by flash chromatography (5:1 hexanes/THF eluent) to provide the ketone[57] (1.57 g, 99% yield, R_F = 0.17 in 2:1 CH_2Cl_2/hexanes) as a colorless oil.

To a suspension of potassium *tert*-butoxide (1.63 g, 14.5 mmol) in toluene (53.7 mL) at 0 °C was added (hexyl)triphenylphosphonium bromide (6.20 g, 14.5 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the indolyl ketone (1.08 g, 5.37 mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and

concentrated in vacuo. The resulting oil was purified by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) to provide indole **275** (666 mg, 46% yield, R_F = 0.50 in 9:1 hexanes/EtOAc, 60:40 mixture of olefin isomers) as a clear oil. **Indole 275**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.29-7.23 (m, 1H), 7.29-7.23 (m, 1H), 7.18-7.11 (comp m, 1H), 7.18-7.11 (comp m, 1H), 6.88 (s, 1H), 6.86 (s, 1H), 5.24 (app.q, *J* = 7.1 Hz, 1H), 5.24 (app.q, *J* = 7.1 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.89 (app.t, *J* = 8.5 Hz, 2H), 2.85 (app.t, *J* = 8.0 Hz, 2H), 2.48-2.39 (comp m, 2H), 2.48-2.39 (comp m, 2H), 2.05 (app.q, *J* = 6.9 Hz, 2H), 2.00 (app.q, *J* = 6.9 Hz, 2H), 1.83 (s, 3H), 1.74 (s, 3H), 1.40-1.23 (comp m, 6H), 1.43-1.23 (comp m, 6H), 0.94 (t, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 135.1, 128.1, 126.2, 125.3, 121.6, 119.2, 118.7, 115.5, 109.3, 40.7, 33.1, 32.7, 31.8, 30.0, 29.8, 28.1, 24.2, 24.0, 23.7, 22.9, 16.3, 14.3; IR (film) 2924, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{19}H_{27}N]^+$: 269.2143, found 269.2136.



245 *277*

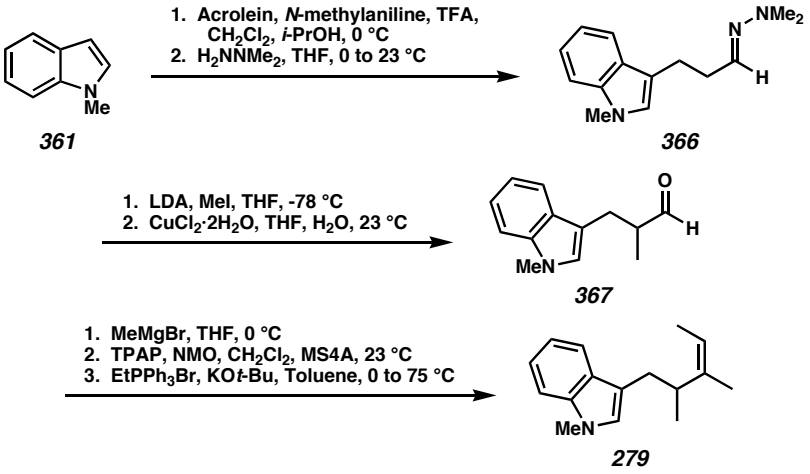
Indole 277. To a solution of indole (5.00 g, 42.7 mmol) in 85.4 mL CH_2Cl_2 at 23 °C was added methyl vinyl ketone (3.55 mL, 42.7 mmol) and $InCl_3$ (944 mg, 4.27 mmol). The reaction mixture was stirred at 23 °C for 4 h, quenched with water (160 mL), and extracted with CH_2Cl_2 (2 x 200 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to a brown solid. The solid was dissolved in CH_2Cl_2 and passed through a plug of SiO_2 (5 x 5 cm, 4:1 CH_2Cl_2/hexanes eluent). The filtrate was

evaporated to provide the ketone[50] (6.49 g, 81% yield, R_F = 0.22 in 100% CH_2Cl_2) as a white solid.

To a suspension of potassium *tert*-butoxide (7.50 g, 66.8 mmol) in toluene (267 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (24.8 g, 66.8 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the indolyl ketone (5.00 g, 26.7 mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (250 mL, 1:1), and extracted with EtOAc (2 x 250 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin[51] (4.31 g, 81% yield, R_F = 0.67 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (982 mg, 4.93 mmol) in THF (19.7 mL) at 0 °C was added NaH (394 mg, 60% dispersion in mineral oil, 9.86 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with benzyl bromide (880 μl, 7.40 mmol), and allowed to warm to 23 °C. After 4 h, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (100 mL), and extracted with ether (2 x 250 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide benzyl indole **277** (872 mg, 61% yield, R_F = 0.42 in 9:1 hexanes/EtOAc, 57:43 mixture of olefin isomers) as a clear oil. **Indole 277**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.6 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.33-7.26 (comp m, 4H), 7.33-7.26 (comp m, 4H), 7.22-7.11 (comp m,

4H), 7.22-7.11 (comp m, 4H), 6.95 (s, 1H), 6.92 (s, 1H), 5.34-5.24 (m, 1H), 5.34-5.24 (m, 1H), 5.30 (s, 2H), 5.30 (s, 2H), 2.89 (t, J = 8.2 Hz, 2H), 2.86 (t, J = 8.2 Hz, 2H), 2.49-2.39 (comp m, 2H), 2.49-2.39 (comp m, 2H), 1.80 (s, 3H), 1.72 (s, 3H), 1.61 (d, J = 7.1 Hz, 3H), 1.56 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 136.9, 136.2, 136.0, 128.9, 128.4, 127.7, 127.0, 125.5, 121.8, 119.5, 119.3, 119.0, 116.2, 109.8, 50.0, 40.5, 32.6, 24.2, 23.6, 16.0, 13.6, 13.5; IR (film) 2917, 1467, 1453, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{21}H_{23}N]^+$: 289.1830, found 289.1820.



Indole 279. To a solution of acrolein (4.62 mL, 70.5 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (179 μl, 1.65 mmol) and trifluoroacetic acid (127 μl, 1.65 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h, then filtered through a pad of silica gel (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (6:1 hexanes/EtOAc eluent) provided the aldehyde[53] (3.54 g, 80% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a yellow oil.

Aldehyde alkylation was accomplished using dimethylhydrazone chemistry according to the procedure of Corey and Enders.[58] To a solution of the aldehyde (2.00 mL, 11.6 mmol) in THF (58 mL) at 0 °C was added 1,1-dimethylhydrazine (973 μl, 12.8 mmol) dropwise. The resulting solution was stirred at 0 °C for 30 min, then allowed to warm to 23 °C, and was stirred overnight (12 h). The solution was concentrated to an oil, which was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide hydrazone **366** (1.84 g, 69% yield, R_F = 0.41 in 1:1 hexanes/EtOAc) as a yellow oil.

To a solution of LDA (26.0 mmol) in THF (13.7 mL) at –78 °C was added the hydrazone (5.43 g, 23.7 mmol) in THF (10 mL) dropwise via cannula. The reaction mixture was allowed to warm to 0 °C, and was stirred 2.5 h. The mixture was then cooled to –78 °C, and methyl iodide (2.30 mL, 37.0 mmol) was added. After 1 h, the reaction was quenched by quick addition of saturated NH_4Cl (75 mL) and Et_2O (75 mL). The mixture was allowed to warm to 23 °C, the phases were separated, and the aqueous phase extracted with Et_2O (2 x 75 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the α-methyl dimethylhydrazone (3.64 g, 63% yield, R_F = 0.52 in 1:1 hexanes/EtOAc) as a yellow oil.

The dimethylhydrazone was converted to the aldehyde by the procedure outlined by Yamashita et al.[59] To a solution of copper(II) chloride dihydrate (2.81 g, 16.5 mmol) in water (150 mL) at 23 °C was added a solution of the α-methyl dimethylhydrazone (3.64 g, 15.0 mmol) in THF (224 mL). The reaction was stirred vigorously for 16 h, then quenched with 3.0 M NH_4OH. EtOAc (200 mL) was added, the phases were separated, and the aqueous layer was extracted with EtOAc (1 x 150 mL). The combined organic

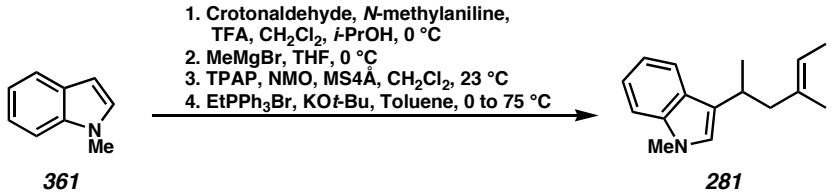
phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 to 1:1 hexanes/EtOAc eluent) afforded aldehyde **367** (1.85 g, 61% yield, R_F = 0.67 in 2:1 hexanes/EtOAc) as a clear oil.

To a solution of **367** (1.85 g, 9.19 mmol) in THF (18.4 mL) at 0 °C was added methylmagnesium bromide (3.67 mL, 3.0 M in Et_2O, 11.0 mmol) dropwise over 5 min. The reaction was stirred for 30 min, and then quenched with saturated NH_4Cl (30 mL). The reaction mixture was partitioned between Et_2O (100 mL) and water (75 mL), and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the alcohol (1.50 g, 75% yield, R_F = 0.36 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alcohol (593 mg, 2.73 mmol) in CH_2Cl_2 (5.46 mL) at 23 °C was added 4Å molecular sieves (1.36 g, 500 mg/mmol substrate), then NMO (479 mg, 4.09 mmol). The suspension was stirred for 15 min, at which point TPAP (47.8 mg, 0.136 mmol) was added. After stirring 15 min, the reaction mixture was filtered through a pad of silica gel (3 x 7 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. The resulting ketone (374 mg) was used without further purification (R_F = 0.59 in 2:1 hexanes/EtOAc).

To a suspension of potassium *tert*-butoxide (526 mg, 4.69 mmol) in toluene (12.4 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (1.74 g, 4.69 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, a solution of the ketone (from above) in toluene (5.00 mL) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was

cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil (product indole contaminated with PPh_3) was dissolved in THF (10 mL), and to the solution was added methyl iodide (292 µl, 4.69 mmol). After stirring 2 h, the mixture was filtered through a pad of celite (2 x 7 cm, Et_2O eluent), and the filtrate was concentrated to an oil. This oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **279** (290 mg, 47% yield over 2 steps, R_F = 0.61 in 9:1 hexanes/EtOAc, 73:27 mixture of olefin isomers) as a clear oil. **Indole 279**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.23 (app.t, *J* = 7.2 Hz, 1H), 7.23 (app.t, *J* = 7.2 Hz, 1H), 7.12 (app.t, *J* = 7.2 Hz, 1H), 7.12 (app.t, *J* = 7.2 Hz, 1H), 6.83 (s, 1H), 6.82 (s, 1H), 5.31 (q, *J* = 6.8 Hz, 1H), 5.22 (q, *J* = 6.8 Hz, 1H), 3.75 (s, 3H), 3.75 (s, 3H), 3.12 (m, 1H), 2.94-2.59 (comp m, 2H), 2.94-2.59 (comp m, 2H), 2.52 (m, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.61 (d, *J* = 6.6 Hz, 3H), 1.55 (d, *J* = 8.2 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 140.5, 137.1, 128.4, 126.9, 126.8, 121.5, 119.3, 119.2, 118.9, 118.6, 117.6, 114.4, 114.2, 109.2, 43.6, 34.5, 32.8, 31.4, 30.6, 19.5, 18.8, 18.6, 13.5, 13.2, 13.0; IR (film) 2960, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1675.



361 *281*

Indole 281. To a solution of crotonaldehyde (5.83 mL, 70.4 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (178 μl, 1.64 mmol) and trifluoroacetic acid (126 μl, 1.64 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 15 h, then filtered through a pad of SiO_2 (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) provided the aldehyde[60] (3.13 g, 66% yield, R_F = 0.35 in 4:1 hexanes/EtOAc) as a yellow oil.

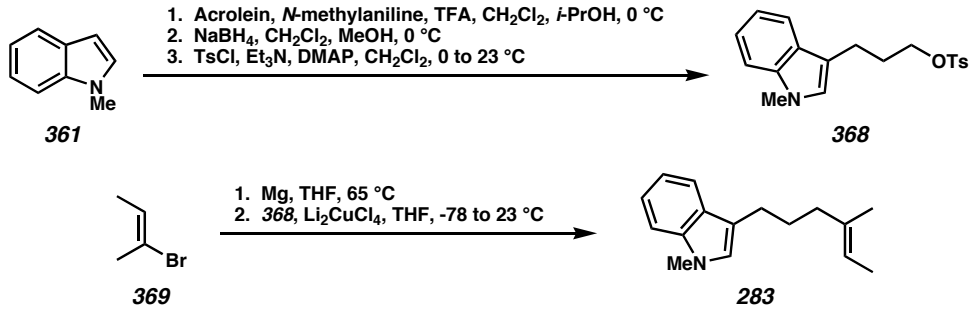
To a solution of the aldehyde (2.85 g, 14.2 mmol) in THF (28.4 mL) at 0 °C was added methylmagnesium bromide (5.67 mL, 3.0 M in Et_2O, 17.0 mmol) dropwise over 5 minutes. The reaction was stirred for 30 min, and then quenched with saturated NH_4Cl (50 mL). The reaction mixture was partitioned between Et_2O (125 mL) and water (75 mL), and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the alcohol (1.53 g, 50% yield, R_F = 0.35 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alcohol (1.50 g, 6.90 mmol) in CH_2Cl_2 (13.8 mL) at 23 °C was added 4Å molecular sieves (3.45 g, 500 mg/mmol substrate), then NMO (1.22 g, 10.4 mmol). The suspension was stirred for 15 min, at which point TPAP (121 mg, 0.345 mmol) was added. After stirring 15 min, the reaction mixture was filtered through a pad

of SiO_2 (5 x 7 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. The resulting ketone[61] (1.28 g, R_F = 0.57 in 2:1 hexanes/EtOAc) was used without further purification.

To a suspension of potassium *tert*-butoxide (1.81 g, 16.1 mmol) in toluene (49.5 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (5.98 g, 16.1 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, a solution of the ketone (1.28 g, 5.95 mmol) in toluene (10 mL) was added, and the solution was heated to 75 °C. After stirring for 9 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (150 mL, 1:1), and extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil (product indole contaminated with PPh_3) was dissolved in THF (32 mL), and to the solution was added methyl iodide (1.00 mL, 16.1 mmol). After stirring 2 h, the mixture was filtered through a pad of celite (3 x 7 cm, Et_2O eluent), and the filtrate was concentrated to an oil. This oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **281** (1.35 g, 99% yield, R_F = 0.65 in 4:1 hexanes/EtOAc, 53:47 mixture of olefin isomers) as a clear oil. **Indole 281**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.1 Hz, 1H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.13 (app.t, *J* = 7.4 Hz, 1H), 7.13 (app.t, *J* = 7.4 Hz, 1H), 6.88 (s, 1H), 6.84 (s, 1H), 5.35 (q, *J* = 6.6 Hz, 1H), 5.30 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.27 (m, 1H), 3.27 (m, 1H), 2.59 (br dd, *J* = 4.7, 13.4 Hz, 1H), 2.47 (app.d, *J* = 7.2 Hz, 1H), 2.47 (app.d, *J* = 7.2 Hz, 1H), 2.20 (app.dd, *J* = 9.9, 13.2 Hz, 1H), 1.79 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 135.3, 134.8, 127.4, 124.9, 124.8, 121.6, 120.6, 120.4, 120.3, 119.6, 118.6, 109.4, 48.5, 39.9, 32.8, 29.3, 28.9, 23.9, 20.7, 15.8, 13.8, 13.6; IR (film) 2960, 1473, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1676.



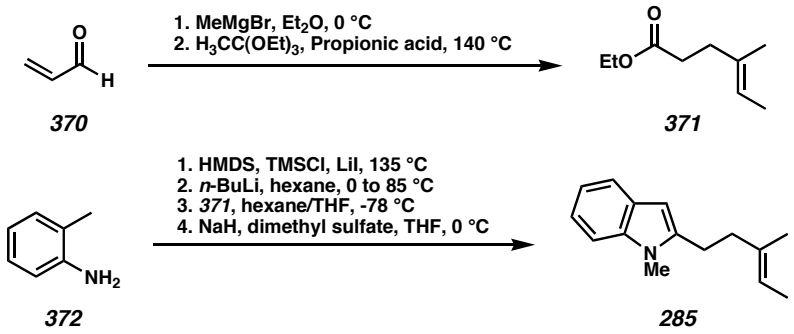
Indole 283. To a solution of acrolein (4.62 mL, 70.5 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (179 μl, 1.65 mmol) and trifluoroacetic acid (127 μl, 1.65 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h, then filtered through a pad of silica gel (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (6:1 hexanes/EtOAc eluent) provided the aldehyde[53] (3.54 g, 80% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a yellow oil.

To a solution of the aldehyde (2.00 mL, 11.6 mmol) in 1:1 CH_2Cl_2/MeOH (11.6 mL) at 0 °C was added $NaBH_4$ (526 mg, 13.9 mmol) in four portions over 10 min. The resulting solution was quenched at 0 °C with 1.0 M HCl and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to an oil, which was used immediately without further purification (R_F = 0.28 in 2:1 hexanes/EtOAc).

The oil was dissolved in CH_2Cl_2 (58 mL), cooled to 0 °C, and treated with tosyl chloride (3.32 g, 17.4 mmol), triethylamine (3.23 mL, 23.2 mmol), and DMAP (142 mg, 1.16 mmol), sequentially. The solution was allowed to warm to 23 °C and stirred 10 h. The mixture was cooled to 0 °C and quenched with saturated NH_4Cl (75 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 75 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (1:1 hexanes/CH_2Cl_2 eluent) afforded tosylate **368** (2.62 g, 66% yield over 2 steps, R_F = 0.59 in 2:1 hexanes/EtOAc) as a colorless oil.

Copper-catalyzed coupling of vinyl Grignard reagents with alkyl sulfonates was accomplished using the procedure outlined by Foquet and Schlosser.[62] To a stirring suspension of magnesium turnings (260 mg, 10.7 mmol) in THF (21.4 mL) at 23 °C was added 2-bromo-2-butene (1.09 mL, 10.7 mmol). The mixture was heated to 65 °C and stirred 1 h, at which point the Grignard reagent had been fully generated. The solution was cooled to 23 °C, and then added via syringe to a solution of **368** (2.62 g, 7.63 mmol) in THF (7.63 mL) at –78 °C. Lithium tetrachlorocuprate (763 μl, 0.1 M in THF, 0.0763 mmol) was then added, and the reaction mixture was allowed to warm to 23 °C. After stirring for 32 h, the reaction was cooled to 0 °C and quenched by slow addition of 1.0 N HCl. The mixture was partitioned between 150 mL Et_2O and 150 mL H_2O. The organic phase was washed with H_2O (100 mL), and the aqueous layers were combined and extracted with Et_2O (150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (30:1 hexanes/Et_2O eluent) provided indole **283** (1.35 g, 78% yield, R_F =

0.63 in 4:1 hexanes/Et_2O, single olefin isomer of undetermined geometry) as a clear oil. **Indole 283**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (app.t, *J* = 7.3 Hz, 1H), 7.12 (app.t, *J* = 7.7 Hz, 1H), 6.86 (s, 1H), 5.27 (q, *J* = 6.4 Hz, 1H), 3.76 (s, 3H), 2.77 (t, *J* = 8.0 Hz, 2H), 2.18 (t, *J* = 7.7 Hz, 2H), 1.83 (comp m, 2H), 1.74 (s, 3H), 1.60 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 136.3, 128.2, 126.1, 121.6, 119.3, 119.2, 118.7, 115.6, 109.3, 32.7, 31.6, 28.7, 25.2, 23.6, 13.5; IR (film) 2930, 1473, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1680.



Indole 285. To a solution of MeMgBr (4.43 mL, 3.0 M in Et_2O, 13.3 mmol) in Et_2O (4 mL) at 0 °C was added methacrolein (1.00 mL, 12.1 mmol) in Et_2O (7 mL) dropwise via cannula. After 30 min, the reaction was quenched by dropwise addition of 1.0 N HCl (15 mL) and extracted with Et_2O (3 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to a colorless oil, which was carried on without further purification.

The allylic alcohol (assume 12.1 mmol) was dissolved in triethylorthoacetate (15.5 mL, 84.7 mmol), and the solution was treated with propionic acid (271 μl, 3.63 mmol). The reaction was heated to 140 °C with distillative removal of ethanol. After

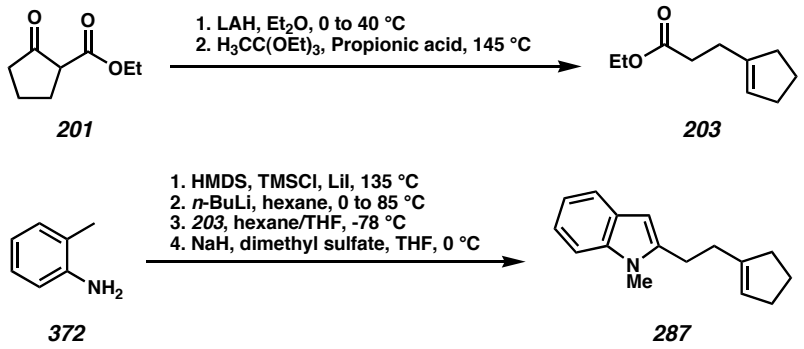
distillation was complete, the reaction was stirred at 140 °C for an additional 60 min, then cooled to 23 °C and diluted with ether (100 mL). The solution was stirred with 1.0 M aq. $KHSO_4$ (100 mL) for 8 h. The phases were separated, and the aqueous phase was extracted with ether (1 x 75 mL). The organic layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (3:2 hexanes/CH_2Cl_2 eluent) provided ester **371**[63] (895 mg, 47% yield over 2 steps, R_F = 0.33 in 1:1 hexanes/CH_2Cl_2) as a colorless oil.

2-substituted indoles were synthesized according to the procedure of Smith et al.[64] A 50 mL flask was charged with hexamethydisilazane (17.7 mL, 84.0 mmol), *o*-toluidine (2.99 mL, 28.0 mmol), TMSCl (197 μl, 1.68 mmol), and lithium iodide (75.0 mg, 0.560 mmol). The mixture was heated to 135 °C and stirred 20 h. The reaction mixture was treated with cyclohexene oxide (1.13 mL, 11.2 mmol) in two equal portions over 15 minutes, then cooled to 23 °C. The volatile materials were removed by distillation under atmospheric pressure. The trimethylsilylaniline was then isolated as a clear oil by vacuum distillation (bp 50 °C at 1 torr).

To a solution of the trimethylsilylaniline (757 μl, 3.88 mmol) in hexane (34.6 mL) at 0 °C was added *n*-butyllithium (3.71 mL, 2.3 M solution in hexane, 8.54 mmol) dropwise. The orange solution was heated to 85 °C and stirred for 6 h. The resulting heterogeneous mixture was cooled to –78 °C and treated with a solution of ester **371** (709 mg, 4.54 mmol) in THF (45.4 mL) quickly. The solution was allowed to warm to 23 °C, stirred 1 h, and quenched with brine. The layers were separated, and the aqueous phase was extracted with 2 x 150 mL Et_2O, 2 x 150 mL EtOAc, and 150 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification

of the oil by flash chromatography (2 columns: 9:1 hexanes/Et_2O eluent, then 3:1 hexanes/CH_2Cl_2 eluent) provided the indole (372 mg, 48% yield, R_F = 0.52 in 4:1 hexanes/EtOAc) as a yellow solid.

To a solution of the indole (116 mg, 0.582 mmol) in THF (2.33 mL) at 0 °C was added NaH (46.4 mg, 60% dispersion in mineral oil, 1.16 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C and treated with dimethyl sulfate (83.1 μl, 0.873 mmol). After 30 min, the reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with ether (2 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by flash chromatography (15:1 hexanes/Et_2O eluent) to provide indole **285** (106 mg, 85% yield, R_F = 0.50 in 9:1 hexanes/EtOAc) as a clear oil. **Indole 285**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.17 (app.t, *J* = 7.4 Hz, 1H), 7.08 (app.t, *J* = 7.7 Hz, 1H), 6.28 (s, 1H), 5.35 (app.q, *J* = 6.6 Hz, 1H), 3.69 (s, 3H), 2.84 (app.t, *J* = 8.2 Hz, 2H), 2.42 (app.t, *J* = 8.2 Hz, 2H), 1.72 (s, 3H), 1.63 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 137.6, 135.1, 128.2, 120.7, 120.0, 119.5, 119.4, 108.9, 98.8, 38.9, 29.6, 26.0, 16.0, 13.6; IR (film) 2917, 1468, 745 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{19}N]^+$: 213.1517, found 213.1514.



Indole 287. To a stirring suspension of lithium aluminum hydride (13.6 g, 359 mmol) in Et_2O (120 mL) at 0 °C was added ethyl 2-oxocyclopentanecarboxylate (25.0 mL, 169 mmol) in Et_2O (50 mL) dropwise via an addition funnel. The reaction mixture was heated to 40 °C and stirred 30 min. The mixture was then cooled to 0 °C and quenched by the slow addition of water. The resulting mixture was diluted with Et_2O (500 mL) and stirred vigorously with 20% aqueous solution of sodium potassium tartrate (150 mL) for 1 h. The phases were then separated, and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to a yellow oil. Fractional distillation of the oil (bp 92 °C at 68 torr) provided the allylic alcohol[65] (6.83 g, 41% yield, R_F = 0.26 in 4:1 hexanes/EtOAc) as a colorless oil.

The allylic alcohol (2.50 mL, 24.3 mmol) was dissolved in triethylorthoacetate (35.6 mL, 194 mmol), and the solution was treated with propionic acid (660 μl, 8.31 mmol). The reaction was heated to 145 °C with distillative removal of ethanol. After distillation was complete, the reaction was stirred at 145 °C for an additional 60 min, then cooled to 23 °C and diluted with Et_2O (300 mL). The solution was stirred with 1.0 M aq. $KHSO_4$ (300 mL) for 8 h. The phases were separated, and the aqueous phase was extracted with ether (1 x 200 mL). The organic layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the

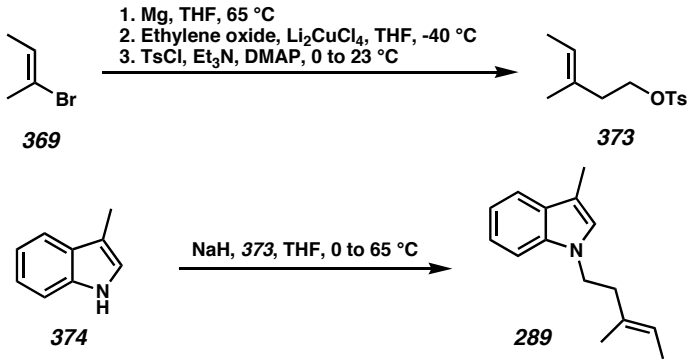
residue by flash chromatography (30:1 hexanes/Et_2O eluent) provided ester **203**[66] (3.22 g, 79% yield, R_F = 0.62 in 4:1 hexanes/Et_2O) as a clear oil.

A 50 mL flask was charged with hexamethydisilazane (17.7 mL, 84.0 mmol), *o*-toluidine (2.99 mL, 28.0 mmol), TMSCl (197 μl, 1.68 mmol), and lithium iodide (75.0 mg, 0.560 mmol). The mixture was heated to 135 °C and stirred 20 h. The reaction mixture was treated with cyclohexene oxide (1.13 mL, 11.2 mmol) in two equal portions over 15 minutes, then cooled to 23 °C. The volatile materials were removed by distillation under atmospheric pressure. The trimethylsilylaniline was then isolated as a clear oil by vacuum distillation (bp 50 °C at 1 torr).

To a solution of the trimethylsilylaniline (408 μl, 2.09 mmol) in hexane (18.7 mL) at 0 °C was added *n*-butyllithium (2.00 mL, 2.3 M solution in hexane, 4.60 mmol) dropwise. The orange solution was heated to 85 °C and stirred for 6 h. The resulting heterogeneous mixture was cooled to –78 °C and treated with a solution of ester **203** (412 mg, 2.45 mmol) in THF (24.5 mL) quickly. The solution was allowed to warm to 23 °C, stirred 1 h, and quenched with brine. The layers were separated, and the aqueous phase was extracted with 2 x 100 mL Et_2O, 2 x 100 mL EtOAc, and 100 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (2 columns: 4:1 hexanes/CH_2Cl_2 eluent, then 9:1 hexanes/Et_2O eluent) provided the indole (172 mg, 39% yield, R_F = 0.56 in 4:1 hexanes/EtOAc) as a white solid.

To a solution of the indole (139 mg, 0.658 mmol) in THF (2.63 mL) at 0 °C was added NaH (52.8 mg, 60% dispersion in mineral oil, 1.32 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to

0 °C and treated with dimethyl sulfate (94.0 μl, 0.987 mmol). After 30 min, the reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with ether (2 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) to provide indole **287** (127 mg, 86% yield, R_F = 0.57 in 4:1 hexanes/EtOAc) as a white solid. **Indole 287**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.16 (app.t, *J* = 7.4 Hz, 1H), 7.07 (app.t, *J* = 7.4 Hz, 1H), 6.28 (s, 1H), 5.47 (m, 1H), 3.69 (s, 3H), 2.93-2.88 (comp m, 2H), 2.54-2.49 (comp m, 2H), 2.37 (comp m, 4H), 1.91 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 141.4, 137.5, 128.1, 124.3, 120.7, 120.0, 119.4, 108.9, 98.8, 35.5, 32.7, 30.5, 29.6, 25.6, 23.7; IR (film) 2842, 1468, 744 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1513.



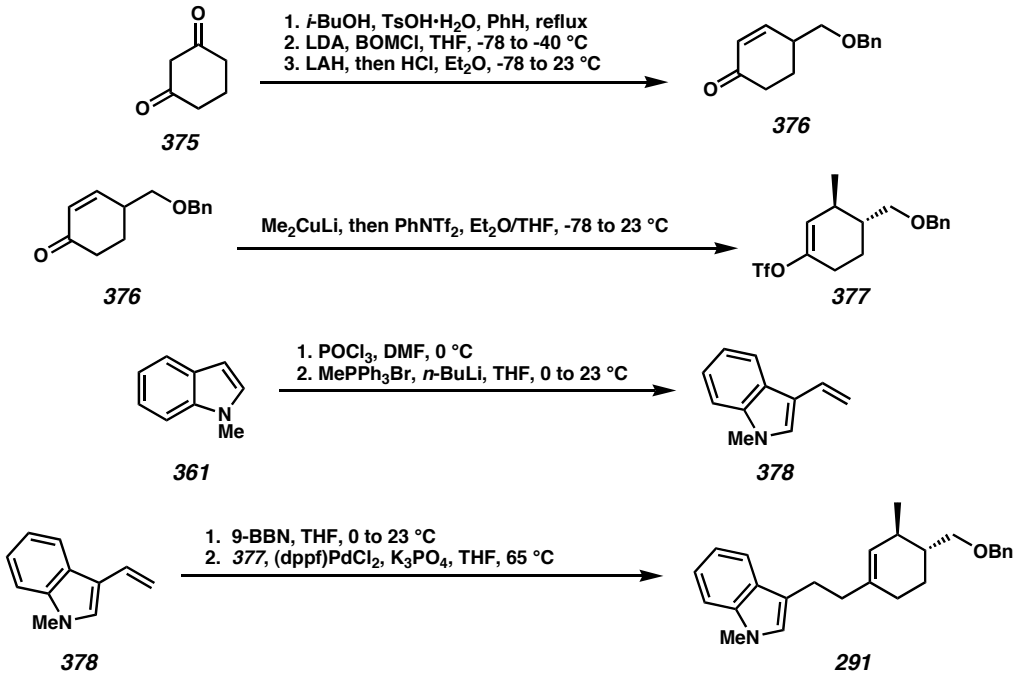
Indole 289. To a stirring suspension of magnesium turnings (146 mg, 6.00 mmol) in THF (12 mL) at 23 °C was added 2-bromo-2-butene (610 μl, 6.00 mmol). The mixture was heated to 65 °C and stirred 1 h, at which point the Grignard reagent had been fully generated. The solution was cooled to 23 °C, and then added via syringe to a solution of ethylene oxide (300 μl, 6.00 mmol) in THF (12 mL) at –40 °C. Lithium

tetrachlorocuprate (3.00 mL, 0.1 M in THF, 0.300 mmol) was then added, and the reaction mixture was stirred at –40 °C for 8 h. The reaction was then quenched by the addition of saturated NH_4Cl (30 mL), allowed to warm to 23 °C, and partitioned between 100 mL Et_2O and 100 mL water. The aqueous phase was extracted with Et_2O (1 x 100 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The resulting homoallylic alcohol[67] (R_F = 0.28 in 4:1 hexanes/EtOAc) was used without further purification.

The alcohol (assume 6.00 mmol) was dissolved in CH_2Cl_2 (30 mL), cooled to 0 °C, and treated with tosyl chloride (1.72 g, 9.00 mmol), Et_3N (1.67 mL, 12.0 mmol), and DMAP (73.3 mg, 0.600 mmol), sequentially. The solution was allowed to warm to 23 °C and stirred 12 h. The mixture was cooled to 0 °C and quenched with saturated NH_4Cl (30 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 40 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 hexanes/CH_2Cl_2 eluent) afforded tosylate **373**[68] (458 mg, 30% yield over 2 steps, R_F = 0.46 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of 3-methylindole (227 mg, 1.73 mmol) in THF (5.00 mL) at 0 °C was added NaH (138 mg, 60% dispersion in mineral oil, 3.46 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C and treated with alkyl tosylate **373** (483 mg, 1.90 mmol) in THF (1.92 mL). The reaction was heated to 65 °C and stirred 8 h. The reaction was cooled to 0 °C, quenched with saturated NH_4Cl (50 mL), and extracted with ether (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The

resulting solid was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **289** (259 mg, 70% yield, R_F = 0.82 in 4:1 hexanes/EtOAc, single olefin isomer of undetermined geometry) as a clear oil. **Indole 289**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.14 (app.t, *J* = 7.7 Hz, 1H), 5.35 (q, *J* = 6.6 Hz, 1H), 4.12 (t, *J* = 7.7 Hz, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.37 (s, 3H), 1.77 (s, 3H), 1.46 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 132.5, 129.0, 125.6, 122.1, 121.5, 119.2, 118.6, 110.3, 109.2, 44.5, 32.8, 23.8, 13.4, 9.8; IR (film) 2918, 1468, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{19}N]^+$: 213.1517, found 213.1513.



Trifluoromethanesulfonate 377. To a solution of 1,3-cyclohexanedione (10.0 g, 89.2 mmol) and isobutyl alcohol (25.0 mL, 270 mmol) in benzene (110 mL) at 23 °C was added TsOH•H_2O (77.0 mg, 0.446 mmol). The reaction was heated to reflux with azeotropic removal of water. After 4.5 h, the solution was concentrated to an oil and

distilled (bp 93 °C at 1 torr) to provide the vinylogous ester[69] (14.6 g, 97% yield, R_F = 0.23 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of LDA (7.50 mmol) in THF (10.1 mL) at –78 °C was added a solution of the vinylogous ester (1.00 mL, 6.25 mmol) in THF (10 mL) dropwise via cannula. The reaction mixture was stirred at –78 °C for 2 h, at which point benzyl chloromethyl ether (1.30 mL, 9.38 mmol) was added. The reaction was allowed to warm to –40 °C over 1 h, then stirred at –40 °C for 4 h. The reaction mixture was then quenched by quick addition of saturated $NaHCO_3$ (50 mL) and allowed to warm to 23 °C. Et_2O (75 mL) was added, the phases were separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the alkylated vinylogous ester (1.32 g, 73% yield, R_F = 0.45 in 2:1 hexanes/EtOAc) as a colorless oil.

To a stirring suspension of LAH (115 mg, 3.02 mmol) in Et_2O (11 mL) at –78 °C was added a solution of the vinylogous ester (1.16 g, 4.02 mmol) in Et_2O (5.0 mL) via cannula. The cold bath was removed, and the reaction mixture was allowed to warm over 30 min. The reaction was then cooled to 0 °C, and to the mixture was added slowly 115 μl water, 115 μl, 15% aq. NaOH, and 345 μl water, sequentially. Et_2O (30 mL) was added, and the heterogeneous mixture was stirred for 30 min at 23 °C, at which point a white precipitate had formed. The mixture was filtered through a pad of celite (Et_2O eluent), and to the filtrate was added 1.0 N HCl (25 mL). The biphasic solution was stirred vigorously for 1 h. The phases were separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with

saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated to an oil. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded enone **376**[70] (654 mg, 75% yield, R_F = 0.41 in 2:1 hexanes/EtOAc) as a colorless oil.

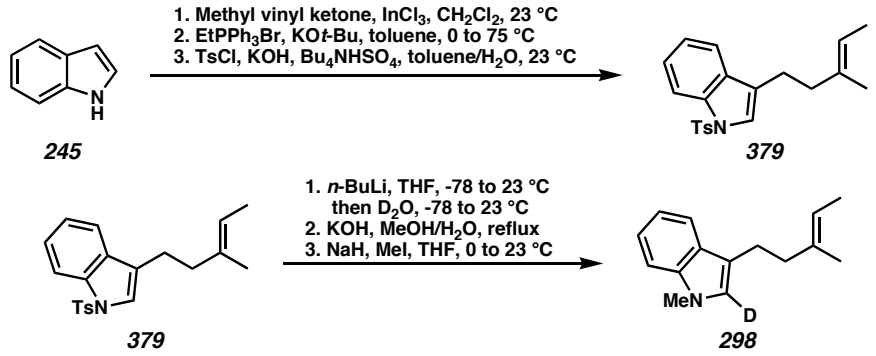
Trifluoromethanesulfonate **377** was generated regioselectively by the procedure of McMurry and Scott.[71] To a stirring suspension of copper(I) iodide (159 mg, 0.833 mmol) in Et_2O (14.1 mL) at 0 °C was added methyllithium (1.04 mL, 1.6 M in Et_2O, 1.67 mmol) dropwise over 1 min. The pale yellow solution was stirred 30 min, then cooled to –78 °C. A solution of enone **376** (120 mg, 0.555 mmol) in THF (12.3 mL) was added dropwise over 3 min, and the resulting solution was stirred at –78 °C for 45 min and 0 °C for 45 min. A solution of $PhNTf_2$ (208 mg, 0.583 mmol) in THF (9 mL) was added via cannula, and the reaction mixture was stirred at 0 °C for 2 h, then 90 min at 23 °C. The reaction was quenched with saturated NH_4OH (50 mL, saturated with NH_4Cl) and diluted with Et_2O (50 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) afforded the vinyl triflate (**377**) (146 mg, 72% yield, R_F = 0.43 in 9:1 hexanes/EtOAc) as a clear oil. Relative stereochemistry was determined based on similar dimethyl cuprate conjugate additions to 4-substituted enones.[72] **Trifluoromethanesulfonate 377**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (comp m, 5H), 5.58 (br s, 1H), 4.51 (ABq, J = 12.3, Δν = 14.3 Hz, 2H), 3.51 (dd, J = 4.5, 9.3 Hz, 1H), 3.38 (dd, J = 6.9, 9.3 Hz, 1H), 2.42-2.23 (comp m, 3H), 2.06-1.97 (m, 1H), 1.76-1.63 (m, 1H), 1.61-1.51 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 138.5, 128.6, 127.9, 127.8, 123.7, 118.7 (q, J = 318 Hz), 73.4, 72.0, 39.9, 31.7,

26.7, 25.0, 20.1; IR (film) 1416, 1209, 1143 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{16}H_{20}O_4SF_3]^+$: 365.1034, found 365.1036.

Vinyl indole 378. $POCl_3$ (437 μl, 4.69 mmol) was added dropwise to 1.02 mL DMF at 0 °C. The mixture was stirred for 30 min, and then a solution of *N*-methylindole (500 μl, 3.91 mmol) in DMF (3.91 mL) was added dropwise. The mixture turned thick and heterogeneous. The reaction mixture was stirred vigorously for 6 h, then poured over ice water (75 mL). The mixture was basified with 5% aq. NaOH (color changed from red to yellow), and the solution was extracted with EtOAc (3 x 75 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to an oil. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc eluent) afforded the aldehyde[73] as a yellow oil (R_F = 0.27 in 1:1 hexanes/EtOAC), which was carried on to the subsequent reaction.

To a stirring suspension of $MePPh_3Br$ (1.92 g, 5.38 mmol) in 11.5 mL THF at 0 °C was added *n*-BuLi (1.88 mL, 2.4 M in hexane, 4.52 mmol) dropwise. The resulting yellow solution was stirred at 0 °C for 30 min, and then a solution of the aldehyde (assume 3.91 mmol) in THF (5.7 mL) was added dropwise. The reaction mixture was maintained at 0 °C for 20 min, then allowed to warm to 23 °C and stirred 6 h. The mixture was poured into ice water (75 mL) and extracted with Et_2O (2 x 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide the vinyl indole[74] (**378**, 535 mg, 87% yield over 2 steps, R_F = 0.71 in 2:1 hexanes/EtOAc) as a colorless oil. The indole was stored frozen in PhH to prevent decomposition.

Indole 291. Suzuki cross-coupling was carried out according to the procedure of Suzuki et al.[75] 9-BBN dimer (203 mg, 0.830 mmol) was dissolved in THF (1.66 mL) at 23 °C under an argon atmosphere. Once fully in solution, it was cooled to 0 °C, and to the solution was added a solution of indole **378** (261 mg, 1.66 mmol) in THF (1.66 mL). The reaction mixture was warmed to 23 °C and stirred for 3 h. To the solution was then added a solution of triflate **377** (552 mg, 1.51 mmol) in THF (7.55 mL), (dppf)$PdCl_2$ (30.8 mg, 0.0378 mmol), and K_3PO_4 (482 mg, 2.27 mmol), and the reaction was heated to 65 °C. After 5 h, the reaction was cooled to 23 °C and quenched with 1 mL NaOH (3.0 M aq.) and 1 mL 30% H_2O_2, and the resulting mixture was stirred 1 h. The mixture was then partitioned between Et_2O (50 mL) and water (40 mL), and the aqueous phase was extracted with Et_2O (1 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 → 1:1 hexanes/CH_2Cl_2 eluent) afforded Suzuki product **291** (467 mg, 75% yield, R_F = 0.20 in 4:1 hexanes/CH_2Cl_2) as a clear oil. **Indole 291**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.34 (app.d, *J* = 4.4 Hz, 4H), 7.36-7.30 (comp m, 2H), 7.25 (app.t, *J* = 7.4 Hz, 1H), 7.13 (app.t, *J* = 7.4 Hz, 1H), 6.85 (s, 1H), 5.29 (s, 1H), 4.56 (ABq, *J* = 12.1 Hz, Δν = 17.7 Hz, 2H), 3.75 (s, 3H), 3.59 (dd, *J* = 4.4, 9.3 Hz, 1H), 3.38 (dd, *J* = 7.2, 9.3 Hz, 1H), 2.88 (app.t, *J* = 8.0 Hz, 2H), 2.37 (app.t, *J* = 7.7 Hz, 2H), 2.10-1.98 (comp m, 3H), 1.58-1.46 (comp m, 2H), 1.03 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 137.2, 137.1, 128.5, 128.2, 127.7, 127.6, 127.2, 126.1, 121.6, 119.2, 118.7, 115.5, 109.3, 73.8, 73.3, 41.2, 38.6, 32.7, 32.5, 27.7, 25.5, 23.9, 21.0; IR (film) 2921, 1453, 1114, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{26}H_{31}NO]^+$: 373.2406, found 373.2410.



To a solution of indole (5.00 g, 42.7 mmol) in 85.4 mL CH_2Cl_2 at 23 °C was added methyl vinyl ketone (3.55 mL, 42.7 mmol) and $InCl_3$ (944 mg, 4.27 mmol). The reaction mixture was stirred at 23 °C for 4 h, quenched with water (160 mL), and extracted with CH_2Cl_2 (2 x 200 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to a brown solid. The solid was dissolved in CH_2Cl_2 and passed through a plug of SiO_2 (5 x 5 cm, 4:1 CH_2Cl_2/hexanes eluent). The filtrate was evaporated to provide the ketone[50] (6.49 g, 81% yield, R_F = 0.22 in 100% CH_2Cl_2) as a white solid.

To a suspension of potassium *tert*-butoxide (7.50 g, 66.8 mmol) in toluene (267 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (24.8 g, 66.8 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the indolyl ketone (5.00 g, 26.7 mmol) was added as a solid, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (250 mL, 1:1), and extracted with EtOAc (2 x 250 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin[51] (4.31 g, 81% yield, R_F = 0.67 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (730 mg, 3.66 mmol) in toluene (3.66 mL) at 23 °C was added Bu_4NHSO_4 (86.9 mg, 0.256 mmol), aq. KOH (4.57 mL, 50% w/v), and a solution of TsCl (934 mg, 4.90 mmol) in toluene (9.80 mL), sequentially. The biphasic mixture was stirred vigorously for 1 h, then partitioned between EtOAc (125 mL) and H_2O (75 mL). The organic layer was washed with H_2O (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (2:1 → 1:1 hexanes/CH_2Cl_2 eluent) to provide the *N*-tosyl indole (**379**, 1.29 g, 100% yield, R_F = 0.43 in 1:1 hexanes/CH_2Cl_2), which was carried to the subsequent reaction.

To a solution of the *N*-tosyl indole (1.29 g, 3.66 mmol) in THF (14.9 mL) at –78 °C was added *n*-BuLi (3.11 mL, 2.4 M in hexane, 7.46 mmol) dropwise over 5 min. The reaction mixture was allowed to warm to 23 °C and stirred 2 h. The mixture was then cooled to –78 °C, and D_2O (445 μl, 24.6 mmol) was added. The mixture was allowed to warm to 23 °C, stirred for 1.5 h, then diluted with Et_2O (150 mL). The solution was washed with saturated NH_4Cl (50 mL), and the aqueous phase was extracted with Et_2O (1 x 75 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 hexanes/CH_2Cl_2 eluent) afforded the deuterated indole (748 mg, 58% yield, R_F = 0.43 in 1:1 hexanes/CH_2Cl_2), which was taken to the next reaction.

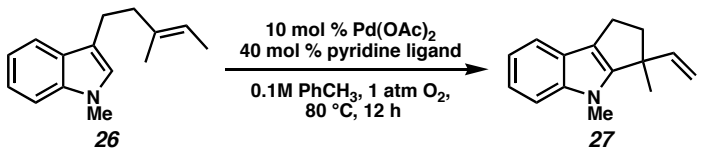
To a solution of the deuterated indole (748 mg, 2.11 mmol) in MeOH (16.5 mL) and H_2O (1.83 mL) at 23 °C was added KOH (3.08 g, 54.9 mmol). The reaction mixture was heated to 75 °C and stirred 1 h. The solution was cooled to room temperature, partitioned between Et_2O (125 mL) and H_2O (75 mL), and the aqueous phase was extracted with Et_2O (2 x 50 mL). The organic phases were combined, washed with brine,

dried over $MgSO_4$, and concentrated in vacuo. The *N*-H indole (R_F = 0.46 in 1:1 hexanes/CH_2Cl_2) was carried to the subsequent reaction without further purification.

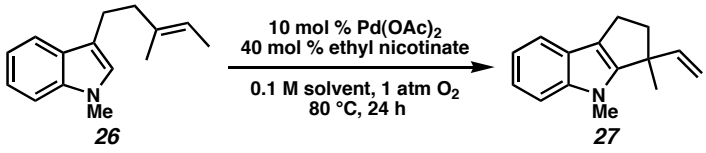
To a solution of the indole (assume 2.11 mmol) in THF (8.44 mL) at 0 °C was added NaH (169 mg, 60% dispersion in mineral oil, 4.22 mmol). The mixture was stirred 15 min at 0 °C, then allowed to warm to 23 °C and stirred an additional 45 min. The reaction was then cooled to 0 °C and treated with MeI (197 μl, 3.17 mmol). The reaction was allowed to warm to 23 °C and stirred 30 min. It was then quenched at 0 °C with D_2O (1 mL) and partitioned between Et_2O (100 mL) and saturated NH_4Cl (60 mL). The aqueous phase was extracted with Et_2O (50 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the *N*-methyl indole (355 mg, 79% yield, R_F = 0.51 in 9:1 hexanes/CH_2Cl_2) as a colorless oil. Deuterium incorporation was measured to be 90% by ^{1}H NMR.

Indole 298. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.31 (app.t, *J* = 8.4 Hz, 1H), 7.31 (app.t, *J* = 8.4 Hz, 1H), 7.25 (app.d, *J* = 8.1 Hz, 1H), 7.25 (app.d, *J* = 8.1 Hz, 1H), 7.18-7.12 (m, 1H), 7.18-7.12 (m, 1H), 5.35 (q, *J* = 6.6 Hz, 1H), 5.31 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.92-2.83 (comp m, 2H), 2.92-2.83 (comp m, 2H), 2.50-2.40 (comp m, 2H), 2.50-2.40 (comp m, 2H), 1.82 (s, 3H), 1.75 (s, 3H), 1.65 (d, *J* = 6.6 Hz, 3H), 1.61 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.2, 136.2, 128.1, 126.1, 125.8 (t, *J* = 26.9 Hz), 121.6, 121.6, 119.5, 119.2, 119.2, 118.7, 118.7, 115.5, 115.4, 109.3, 109.3, 40.7, 32.7, 32.7, 24.2, 23.7, 23.6, 16.0, 13.6, 13.5; IR (film) 2915, 1469, 1373, 738 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{18}ND]^+$: 214.1580, found 214.1574.

4.7.3 Palladium-Catalyzed Indole Annulations



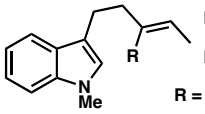
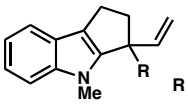
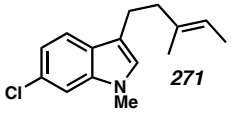
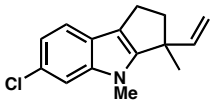
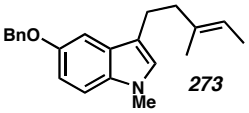
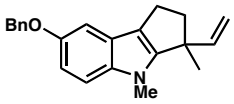
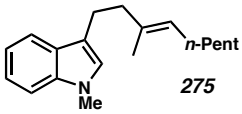
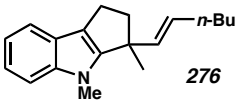
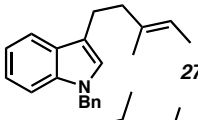
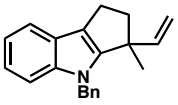
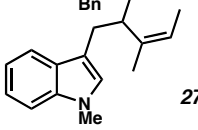
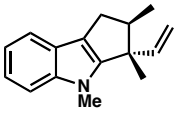
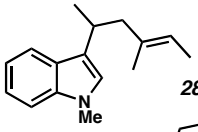
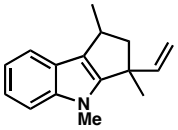
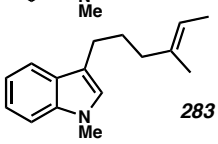
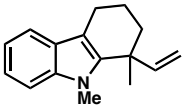
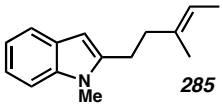
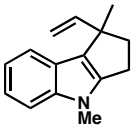
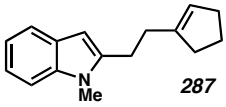
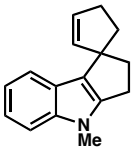
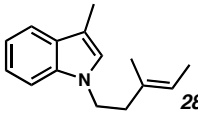
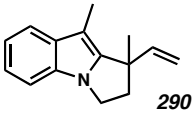
General procedure for the optimization of pyridine ligand (Table 4.3.1): A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by toluene (1.63 mL) and ligand (0.0732 mmol, 0.40 equiv). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **26** (40.0 μl, 0.183 mmol) in toluene (200 μl), and then tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2 for 12 h. An aliquot (approx. 200 μl) was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.



General procedure for the optimization of solvent (Table 4.3.2): A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by solvent (1.63 mL) and ethyl nicotinate (10.0 μl, 0.0732 mmol). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **26** (40.0 μl, 0.183 mmol) in solvent (200 μl), and then tridecane (25.0 μl, 0.103 mmol, internal

standard) were then added via syringe, and the reaction was stirred under O_2 for 24 h. An aliquot (approx. 200 μl) was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Table 4.3.3 (reproduced). The palladium-catalyzed oxidative indole cyclization.[a]

entry	substrate[b]	product	time	% yield[c]
1	 R = Me *26*	 R = Me *27*	24 h	82
2	R = Et *267*	R = Et *268*	18 h	74
3	R = CH_2OBn *269*	R = CH_2OBn *270*	24 h	60
4	 *271*	 *272*	32 h	62
5	 *273*	 *274*	20 h	73
6	 *275*	 *276*	30 h	79[d]
7	 *277*	 *278*	48 h	69
8	 *279*	 *280*	18 h	76 (6:1 dr)
9	 *281*	 *282*	53 h	64 (1:1 dr)
10	 *283*	 *284*	39 h	66[e]
11	 *285*	 *286*	6 h	73[f]
12	 *287*	 *288*	5 h	68[f]
13	 *289*	 *290*	18 h	74

[a] 10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 1 atm O_2, 80 °C, 0.1 M substrate in *t*-amyl alcohol:AcOH (4:1). [b] Typically used as a mixture of olefin isomers. [c] Isolated yields. [d] Product isolated as a 58:42 mixture of *E* and *Z* isomers. [e] 0.1 M in pinacolone. [f] 0.1 M in *t*-amyl alcohol.

General procedure for the oxidative annulation of indoles (Entry 1 is used as an example): A flame-dried 25 mL round bottom flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (17.2 mg, 0.0769 mmol, 0.100 equiv), *t*-amyl alcohol (5.15 mL), acetic acid (1.54 mL), and ethyl nicotinate (42.0 μl, 0.308 mmol, 0.400 equiv), sequentially. The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole (164 mg, 0.769 mmol) in *t*-amyl alcohol (1.00 mL) was then added via syringe, and the reaction was stirred under O_2 for the listed time. Filtration of the reaction mixture through a small pad of silica gel (1 x 5 cm, EtOAc eluent), concentration, and purification of the oil by flash chromatography afforded pure annulated indole.

Entry 1: 24 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (133 mg, 82% yield, R_F = 0.76 in 4:1 hexanes/acetone) as a clear oil.

Indole 27. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.1 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.16 (app.t, *J* = 8.2 Hz, 1H), 7.09 (app.t, *J* = 7.1 Hz, 1H), 6.09 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.06 (dd, *J* = 1.7, 10.4 Hz, 1H), 4.98 (dd, *J* = 1.7, 17.0 Hz, 1H), 3.64 (s, 3H), 2.83 (app.t, *J* = 6.9 Hz, 2H), 2.57-2.48 (m, 1H), 2.40-2.32 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 145.3, 141.8, 124.1, 120.5, 119.2, 119.0, 117.6, 112.1, 109.5, 46.5, 46.2, 30.2, 24.0, 22.7; IR (film) 1468, 742 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{15}H_{17}N]^+$: 211.1361, found 211.1363.

Entry 2: 18 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (123 mg, 74% yield, R_F = 0.80 in 4:1 hexanes/acetone) as a clear oil.

Indole 268. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.16 (app.t, *J* = 8.2 Hz, 1H), 7.08 (app.t, *J* = 7.7 Hz, 1H), 6.11 (dd, *J* = 10.5, 17.3 Hz, 1H), 5.03 (dd, *J* = 1.1, 10.5 Hz, 1H), 4.89 (dd, *J* = 1.1, 17.3 Hz, 1H), 3.63 (s, 3H), 2.80 (app.t, *J* = 7.2 Hz, 2H), 2.54-2.37 (comp m, 2H), 2.00-1.81 (comp m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 144.8, 142.0, 124.2, 120.4, 119.1, 119.0, 118.9, 112.1, 109.4, 50.9, 42.8, 30.5, 30.4, 23.1, 9.4; IR (film) 2964, 2925, 1466, 738 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1510.

Entry 3: 24 h. Purification of the residue by flash chromatography (9:1 to 4:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (96.5 mg, 60% yield, R_F = 0.63 in 4:1 hexanes/Et_2O) as a clear oil.

Indole 270. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.7 Hz, 1H), 7.36-7.26 (comp m, 6H), 7.19 (app.t, *J* = 7.6 Hz, 1H), 7.11 (app.t, *J* = 7.3 Hz, 1H), 6.20 (dd, *J* = 10.7, 17.6 Hz, 1H), 5.17 (dd, *J* = 1.1, 10.7 Hz, 1H), 5.01 (dd, *J* = 1.1, 17.6 Hz, 1H), 4.54 (ABq, *J* = 12.1 Hz, Δν = 14.2 Hz, 2H), 3.74 (ABq, *J* = 9.1 Hz, Δν = 18.5 Hz, 2H), 3.66 (s, 3H), 2.85 (app.t, *J* = 6.9 Hz, 2H), 2.62-2.53 (m, 1H), 2.49-2.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 142.2, 142.0, 138.5, 128.5, 127.8, 127.7, 124.1, 120.6, 119.2, 119.1, 119.0, 114.2, 109.7, 75.6, 73.7, 51.9, 42.2, 31.3, 22.7; IR (film) 2855, 1467, 739 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{23}NO]^+$: 317.1780, found 317.1774.

Entry 4: 32 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (61.2 mg, 62% yield, R_F = 0.72 in 4:1 hexanes/acetone) as a clear oil.

Indole 272. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.07 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.08 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.97 (dd, *J* = 1.1, 17.0 Hz, 1H), 3.60 (s, 3H), 2.80 (app.t, *J* = 6.9 Hz, 2H), 2.56-2.47 (m, 1H), 2.40-2.31 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 145.0, 142.2, 126.5, 122.7, 119.7, 117.7, 112.3, 109.6, 46.4, 46.3, 30.4, 23.9, 22.6; IR (film) 1471, 1375 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{16}NCl]^+$: 245.0971, found 245.0970.

Entry 5: 20 h. Purification of the residue by flash chromatography (3:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (118 mg, 73% yield, R_F = 0.62 in 4:1 hexanes/Et_2O) as a clear oil.

Indole 274. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (app.d, *J* = 6.6 Hz, 2H), 7.43-7.30 (comp m, 3H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.90 (dd, *J* = 2.2, 8.8 Hz, 1H), 6.08 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.12 (s, 2H), 5.06 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.98 (dd, *J* = 1.1, 17.6 Hz, 1H), 3.61 (s, 3H), 2.80 (app.t, *J* = 6.9 Hz, 2H), 2.55-2.46 (m, 1H), 2.38-2.30 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 149.8, 145.3, 138.2, 137.4, 128.7, 127.9, 127.7, 124.3, 117.2, 112.0, 111.1, 110.1, 103.2, 71.4, 46.4, 46.2, 30.3, 23.9, 22.7; IR (film) 1482, 1204 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{23}NO]^+$: 317.1780, found 317.1774.

Entry 6: 30 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (133 mg, 79% yield, R_F = 0.81 in 4:1 hexanes/EtOAc) as a clear oil.

Indole 276. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.16 (app.t, *J* = 7.7 Hz, 1H), 7.15 (app.t, *J* = 7.7 Hz, 1H), 7.09 (app.t, *J* = 7.7 Hz, 1H), 7.08 (app.t, *J* = 7.7 Hz, 1H), 5.71 (s, 1H), 5.66 (s, 1H), 5.39 (t, *J* = 6.9 Hz, 1H), 5.33 (t, *J* = 6.9 Hz, 1H), 3.64 (s, 3H), 3.64 (s, 3H), 2.81 (app.t, *J* = 6.6 Hz, 2H), 2.81 (app.t, *J* = 6.6 Hz, 2H), 2.54-2.45 (m, 1H), 2.54-2.45 (m, 1H), 2.39-2.31 (m, 1H), 2.39-2.31 (m, 1H), 2.04 (app.q, *J* = 6.6 Hz, 2H), 2.04 (app.q, *J* = 6.6 Hz, 2H), 1.48 (s, 3H), 1.48 (s, 3H), 1.37-1.30 (comp m, 4H), 1.37-1.30 (comp m, 4H), 0.90 (app.t, *J* = 7.1 Hz, 3H), 0.90 (app.t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 141.8, 137.1, 128.2, 124.2, 120.3, 119.1, 118.9, 117.2, 109.4, 47.0, 45.4, 32.4, 32.0, 30.2, 24.8, 22.7, 22.4, 14.2; IR (film) 2927, 1466, 736 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{19}H_{25}N]^+$: 267.1987, found 267.1990.

Entry 7: 48 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (132 mg, 68% yield, R_F = 0.76 in 4:1 hexanes/acetone) as a clear oil.

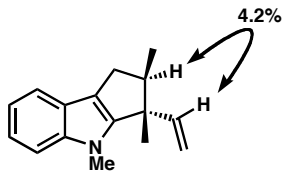
Indole 278. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 1H), 7.29-7.21 (comp m, 4H), 7.12-7.06 (comp m, 3H), 6.99 (app.d, *J* = 7.1 Hz, 2H), 6.04 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.28 (s, 2H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 17.6 Hz, 1H), 2.88 (app.t, *J* = 7.1 Hz, 2H), 2.59-2.50 (m, 1H), 2.40-2.31 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 145.0, 141.6, 138.5, 128.7, 127.2, 126.2, 124.4, 120.8, 119.5, 119.0, 118.1, 112.2,

110.5, 47.4, 46.5, 46.3, 23.9, 22.8; IR (film) 2930, 1453, 739 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{21}H_{21}N]^+$: 287.1674, found 287.1671.

Entry 8: 18 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (109 mg, 76% yield, R_F = 0.78 in 4:1 hexanes/acetone) as a clear oil.

Indole 280. Major diastereomer only: ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.18 (app.t, *J* = 7.7 Hz, 1H), 7.11 (app.t, *J* = 7.7 Hz, 1H), 6.09 (dd, *J* = 11.0, 17.0 Hz, 1H), 5.25 (dd, *J* = 1.4, 11.0 Hz, 1H), 5.24 (dd, *J* = 1.4, 17.0 Hz, 1H), 3.66 (s, 3H), 3.02 (dd, *J* = 7.1, 13.7 Hz, 1H), 2.78 (m, 1H), 2.47 (dd, *J* = 9.3, 13.7 Hz, 1H), 1.22 (s, 3H), 1.12 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 145.2, 141.2, 124.2, 120.4, 119.2, 118.9, 115.9, 113.5, 109.5, 50.3, 48.2, 31.4, 30.0, 17.0, 13.9; IR (film) 2960, 2928, 1464, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1520.

Figure 4.7.1 NOE measurements of the major diastereomer of **280**:



Entry 9: 53 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (94.6 mg, 64% yield, R_F = 0.76 in 4:1 hexanes/acetone) as a clear oil. The indole was isolated as a 55:45 mixture of diastereomers.

Indole 282. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.18 (app.t, *J* = 7.4 Hz, 1H), 7.18 (app.t, *J* = 7.4 Hz, 1H), 7.11 (app.t, *J* = 6.6 Hz, 1H), 7.11 (app.t, *J* = 6.6 Hz, 1H), 6.16 (dd, *J* = 10.2, 17.9 Hz, 1H), 6.05 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.14 (dd, *J* = 1.1, 9.9 Hz, 1H), 5.14 (dd, *J* = 1.1, 17.6 Hz, 1H), 5.00 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.86 (dd, *J* = 1.1, 17.6 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.38 (m, 1H), 3.38 (m, 1H), 2.72 (dd, *J* = 7.7, 12.6 Hz, 1H), 2.55 (dd, *J* = 7.7, 12.6 Hz, 1H), 2.11 (dd, *J* = 6.6, 12.6 Hz, 1H), 1.98 (dd, *J* = 6.6, 12.6 Hz, 1H), 1.59 (s, 3H), 1.47 (s, 3H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.43 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 147.8, 146.5, 145.1, 141.8, 123.9, 122.6, 122.1, 120.5, 119.2, 119.1, 118.7, 112.3, 111.5, 109.6, 109.5, 55.9, 55.8, 46.3, 46.1, 31.8, 31.5, 30.2, 30.1, 25.7, 23.7, 21.9, 21.8; IR (film) 2955, 1466, 740 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1517.

Entry 10: 39 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (98.3 mg, 66% yield, R_F = 0.84 in 4:1 hexanes/acetone) as a clear oil.

Indole 284. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.20 (app.t, *J* = 7.4 Hz, 1H), 7.09 (app.t, *J* = 7.4 Hz, 1H), 6.01 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.14 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.89 (dd, *J* = 1.1, 17.6 Hz, 1H), 3.69 (s, 3H), 2.75 (app.t, *J* = 6.1 Hz, 2H), 1.88-1.70 (comp m, 4H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 139.3, 137.7, 126.9, 121.2, 118.8, 118.3, 113.6, 110.5, 108.7, 41.2, 39.3, 31.7, 25.4, 22.0, 20.0; IR (film) 2929, 1471, 738 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1509.

Entry 11: 6 h. Purification of the residue by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (88.8 mg, 73% yield, R_F = 0.65 in 4:1 hexanes/THF) as a white solid.

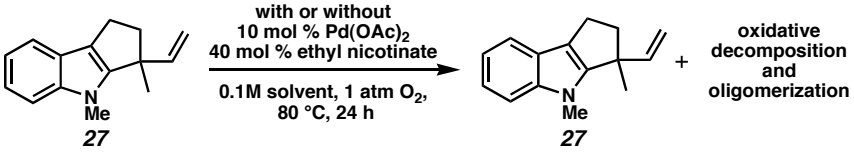
Indole 286. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.14 (app.t, *J* = 7.7 Hz, 1H), 7.06 (app.t, *J* = 7.7 Hz, 1H), 6.15 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.02 (dd, *J* = 1.7, 17.6 Hz, 1H), 4.95 (dd, *J* = 1.7, 10.4 Hz, 1H), 3.68 (s, 3H), 2.89 (app.t, *J* = 6.9 Hz, 2H), 2.55-2.46 (m, 1H), 2.40-2.31 (m, 1H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 145.1, 141.6, 124.0, 122.8, 120.2, 119.1, 118.4, 110.5, 109.7, 46.6, 44.5, 30.9, 26.3, 23.8; IR (film) 2956, 740 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{17}N]^+$: 211.1361, found 211.1367.

Entry 12: 5 h. Purification of the residue by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (75.7 mg, 68% yield, R_F = 0.62 in 4:1 hexanes/THF) as a white solid.

Indole 288. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.13 (app.t, *J* = 7.7 Hz, 1H), 7.05 (app.t, *J* = 7.4 Hz, 1H), 5.84-5.81 (m, 1H), 5.77-5.74 (m, 1H), 3.68 (s, 3H), 2.98-2.82 (comp m, 2H), 2.71-2.43 (comp m, 4H), 2.31-2.22 (m, 1H), 2.07-1.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 141.7, 139.1, 129.0, 123.8, 123.4, 120.2, 119.1, 118.3, 109.6, 56.2, 43.5, 38.0, 32.5, 30.8, 24.3; IR (film) 2942, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{17}N]^+$: 223.1361, found 223.1366.

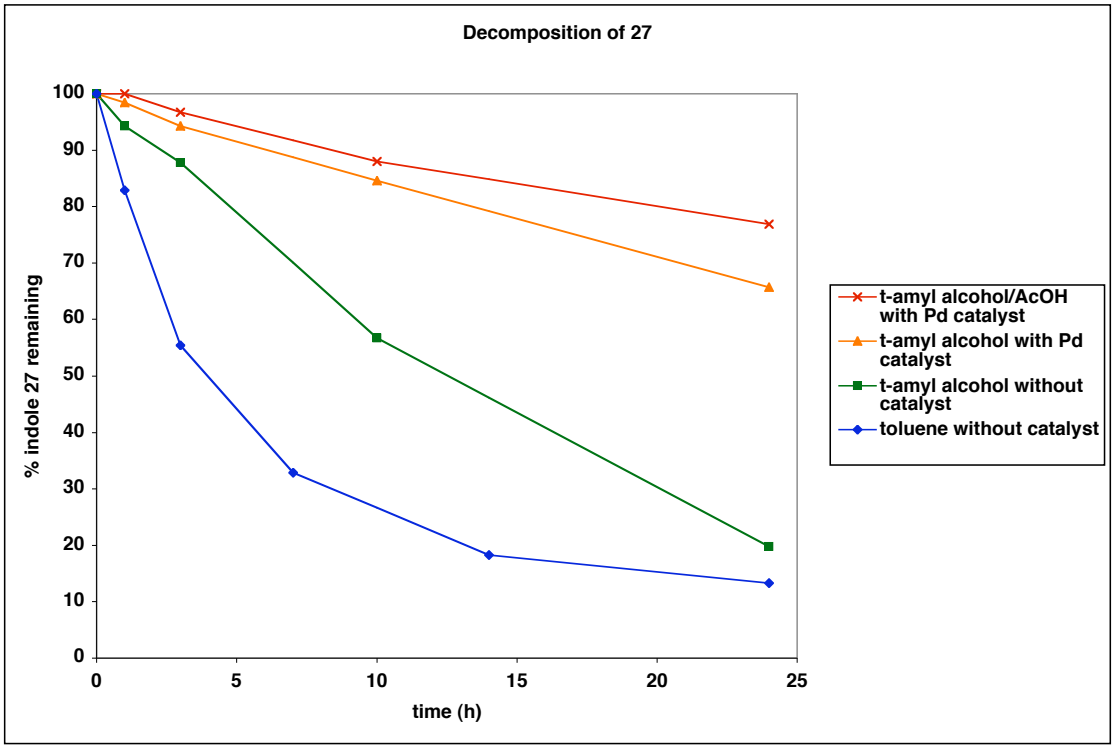
Entry 13: 18 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (114 mg, 74% yield, R_F = 0.45 in 4:1 hexanes/benzene) as a clear oil.

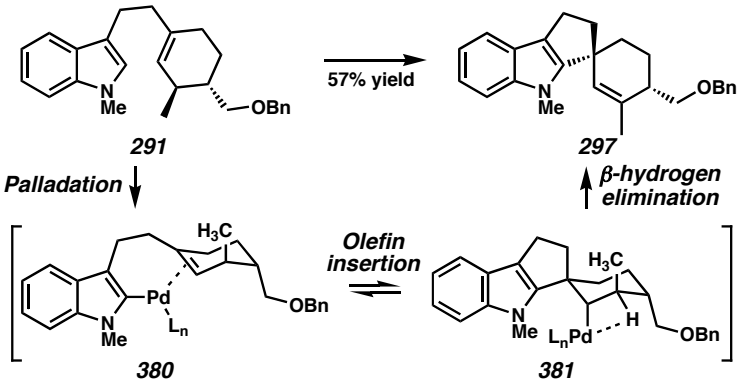
Indole 290. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.16 (app.t, *J* = 7.7 Hz, 1H), 7.10 (app.t, *J* = 7.7 Hz, 1H), 6.06 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.09 (dd, *J* = 1.1, 10.4 Hz, 1H), 5.01 (dd, *J* = 1.1, 17.0 Hz, 1H), 4.10-3.98 (comp m, 2H), 2.61-2.53 (m, 1H), 2.48-2.39 (m, 1H), 2.27 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 143.2, 133.4, 132.2, 120.6, 118.7, 118.6, 112.6, 109.4, 101.6, 44.8, 43.8, 42.0, 24.3, 8.2; IR (film) 2966, 2867, 1461, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{17}N]^+$: 211.1361, found 211.1360.



Control experiments to examine product stability: A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (2.6 mg, 0.0118 mmol) if applicable, followed by solvent (918 μl) and ethyl nicotinate (6.4 μl, 0.0472 mmol) if applicable. The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **27** (25.0 mg, 0.118 mmol) in solvent (200 μl), and then tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2 for 24 h. Aliquots (approx. 200 μl) were withdrawn periodically, filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC. The data collected were plotted on a graph to illustrate decomposition.

Graph from Figure 4.3.1 *(reproduced)*

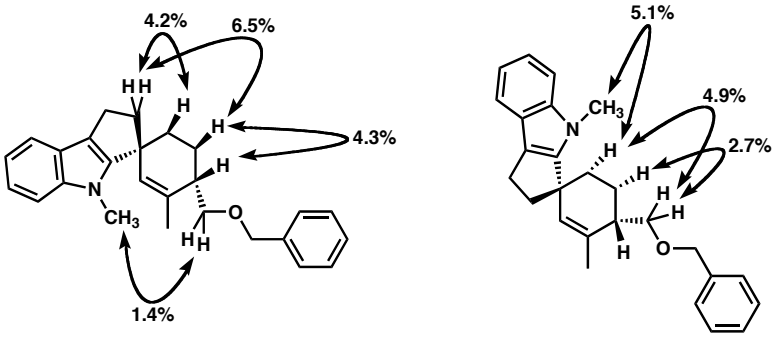


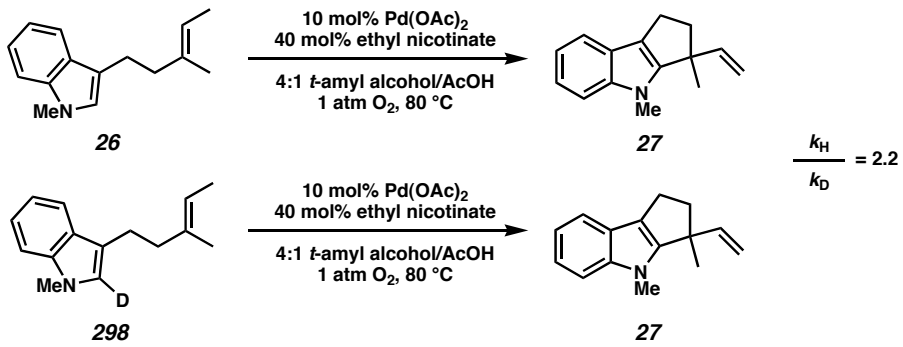


Procedure for the oxidative annulation of diastereomerically pure indole 291. A flame-dried 25 mL round bottom flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.5 mg, 0.0202 mmol) followed by *t*-amyl alcohol (1.52 mL) and ethyl nicotinate (11.0 μl, 0.0808 mmol), sequentially. The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **291** (75.5 mg, 0.202 mmol) in *t*-amyl alcohol (500 μl) was then added via syringe, and the reaction was stirred under O_2 for 24 h. The reaction mixture was filtered through a small pad of silica gel (1 x 5 cm, EtOAc eluent) and concentrated in vacuo. Purification of the oil by flash chromatography (1:1 hexane/PhH eluent) afforded diastereomerically pure annulated indole **297** (42.8 mg, 57% yield, R_F = 0.59 in 4:1 hexanes/Et_2O) as a colorless oil. The relative stereochemistry of the product was determined by NOE analysis. **Indole 297**: ^{1}H NMR (300 MHz, C_6D_6) δ 7.64-7.61 (m, 1H), 7.25-7.20 (comp m, 3H), 7.15-7.09 (comp m, 3H), 7.08-7.02 (comp m, 2H), 5.37 (s, 1H), 4.27 (ABq, *J* = 12.1 Hz, Δν = 22.2 Hz, 2H), 3.43-3.32 (comp m, 2H), 3.14 (s, 3H), 2.77 (dd, *J* = 5.2, 8.0 Hz, 2H), 2.33-2.21 (comp m, 2H), 2.16-2.09 (m, 1H), 1.99-1.91 (m, 1H), 1.83 (dd, *J* = 2.5, 13.5 Hz, 1H), 1.68 (ddd, *J* = 3.3, 5.5, 13.2 Hz, 1H), 1.61 (s, 3H), 1.53 (app.dt, *J* = 2.9, 12.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 141.7, 138.6, 134.4, 130.8, 128.6, 128.0, 127.9, 124.2, 120.2, 119.1, 118.8, 117.1, 109.4, 73.4,

71.4, 44.8, 44.0, 39.0, 30.0, 28.5, 23.7, 23.0, 22.7; IR (film) 2929, 2855, 1466, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{26}H_{29}NO]^+$: 371.2249, found 371.2241.

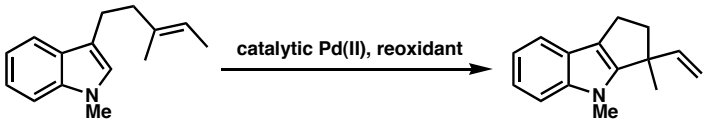
Figure 4.7.2 NOE measurements of annulated indole **297**:





Procedure to examine the kinetic isotope effect: A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by *t*-amyl alcohol (1.26 mL), AcOH (366 μl), and ethyl nicotinate (10.0 μl, 0.0732 mmol). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **26** (40.0 μl, 0.183 mmol) or **298** (39.2 mg, 0.183 mmol) in *t*-amyl alcohol (200 μl), and tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2. Aliquots (approx. 100 μl) were taken hourly, filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Table 4.3.4 (reproduced) Comparison of methods for the oxidative annulation of **26**.



26 ***27***

entry	conditions[a]	ref	% yield[b]
1	$Pd(OAc)_2$, AgOAc, AcOH, air, 110 °C	14a	4
2	$Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, air, 110 °C	14a	0
3	$Pd(OAc)_2$, $K_2S_2O_8$, AcOH, air, 110 °C	14a	0
4	$Pd(OAc)_2$, $NaNO_2$, AcOH, air, 110 °C	14a	0
5	$Pd(OAc)_2$, $Cu(OAc)_2$, Dioxane/AcOH (4:1), O_2, 100 °C	40a	13
6	$Pd(OAc)_2$, benzoquinone, $TsOH{\cdot}H_2O$, Toluene/AcOH (2:1), O_2, 23 °C	40b	0
7	$Pd(OAc)_2$, $H_6PMo_9V_3O_{40}$, acetylacetonate, NaOAc AcOH, O_2, 90 °C	40c	0
8	$Pd(OAc)_2$, cat. benzoquinone, TBHP $AcOH/Ac_2O$ (4:1), 50 °C	15	5
9	$Pd(OAc)_2$, ethyl nicotinate, t-amyl alcohol/AcOH (4:1), O_2, 80 °C		82

Entries 1-4. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (2.1 mg, 0.00917 mmol). The solid was dissolved in AcOH (3.67 mL), and to the solution was added oxidant (0.183 mmol), followed by indole **26** (20.0 μl, 0.0917 mmol) and tridecane (25.0 μl, 0.103 mmol, internal standard). The reaction was heated to 110 °C under air and allowed to stir. Aliquots (approx. 100 μl) were taken at 5 h and at 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC. The GC yield is listed in the table.

Entry 5. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (0.8 mg, 0.00366 mmol). The solid was dissolved in dioxane (1.83 mL) and AcOH (458 μl), and to the solution was added $Cu(OAc)_2$ (66.5 mg, 0.366 mmol), followed by indole **26** (40.0 μl, 0.183 mmol) and tridecane (25.0 μl, 0.103 mmol, internal standard). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated

to 100 °C under O_2, and allowed to stir. Aliquots (approx. 100 μl) were taken at 5 h and at 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC. The GC yield is listed in the table.

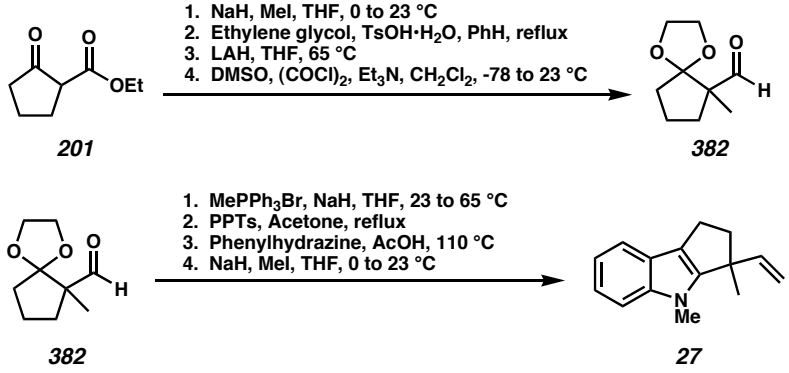
Entry 6. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (0.8 mg, 0.00366 mmol). The solid was dissolved in toluene (137 μl) and AcOH (275 μl), and to the solution was added benzoquinone (19.8 mg, 0.183 mmol), $TsOH•H_2O$ (17.4 mg, 0.0915 mmol), indole **26** (40.0 μl, 0.183 mmol), and tridecane (25.0 μl, 0.103 mmol, internal standard), sequentially. The reaction was stirred at room temperature. Complete decomposition was observed after 5 min.

Entry 7. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by AcOH (485 μl), NaOAc (0.8 mg, 0.00975 mmol), acetylacetonate (1.3 μl, 0.0122 mmol), and $H_6PMo_9V_3O_{40}$ (5.5 mg), sequentially. The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **26** (40.0 μl, 0.183 mmol) in AcOH (125 μl), and then tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2. Aliquots (approx. 100 μl) were taken at 5h and at 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Entry 8. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (0.3 mg, 0.00138 mmol). The solid was dissolved in Ac_2O (91.7 μl) and AcOH (275 μl), and to the solution was added benzoquinone (1.5 mg, 0.0138

mmol), TBHP (50 μl, 70% in H_2O, 0.358 mmol), indole **26** (60.0 μl, 0.275 mmol), and tridecane (25.0 μl, 0.103 mmol, internal standard), sequentially. The flask was heated to 50 °C and allowed to stir. Aliquots (approx. 100 μl) were taken at 5 h and at 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC. The GC yield is listed in the table.

4.7.4 Independent Synthesis



Independent synthesis of annulated indole 27. To a solution of ethyl 2-oxocyclopentanecarboxylate (500 μl, 3.37 mmol) in THF (13.5 mL) at 0 °C was added NaH (162 mg, 60% dispersion in mineral oil, 4.04 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (273 μL, 4.38 mmol), and allowed to warm to 23 °C. After 5 h, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (50 mL), and extracted with ether (2 x 75 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide the ketoester[76] (491 mg, 85% yield, R_F = 0.45 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the ketoester (491 mg, 2.88 mmol) in benzene (8 mL) at 23 °C was added ethylene glycol (321 μl, 5.76 mmol) and TsOH•H_2O (54.8 mg, 0.288 mmol). The reaction mixture was heated to reflux with azeotropic removal of water. After stirring 10 h, the reaction was cooled to room temperature and diluted with Et_2O (75 mL). The solution was washed sequentially with water, saturated $NaHCO_3$, and brine (50 mL each). It was dried over $MgSO_4$, and concentrated to an oil. Purification of the residue

by flash chromatography (6:1 hexanes/EtOAc eluent) afforded the ketal[77] (593 mg, 96% yield, R_F = 0.23 in 4:1 hexanes/Et_2O) as a colorless oil.

To a stirring suspension of LAH (210 mg, 5.54 mmol) in THF (3.5 mL) at 0 °C was added a solution of the ketal (593 mg, 2.77 mmol) in THF (2.5 mL) via cannula. The cold bath was removed, and the reaction mixture was heated to 65 °C and stirred 1 h. The reaction was then cooled to 0 °C, and to the mixture was added slowly 210 μl water, 210 μl NaOH (15% aq. solution), and 630 μl water, sequentially. Et_2O (50 mL) was added, and the heterogeneous mixture was stirred for 30 min at 23 °C, at which point a white precipitate had formed. The mixture was filtered through a pad of celite (Et_2O wash), and the filtrate was concentrated to an oil. The resulting alcohol was used in the next reaction without further purification (R_F = 0.28 in 2:1 hexanes/EtOAc).

To a solution of DMSO (325 μl, 4.58 mmol) in CH_2Cl_2 (7 mL) at –78 °C was added oxalyl chloride (191 μl, 2.19 mmol) dropwise. The reaction mixture was stirred at –78 °C for 45 min, and then crude alcohol (342 mg, 1.99 mmol) in CH_2Cl_2 (2 mL) was added. After stirring for 1.5 h, triethylamine (1.39 mL, 9.95 mmol) was added, and the reaction was allowed to gradually warm to 23 °C over 2 h. The mixture was then diluted with CH_2Cl_2 (40 mL) and quenched with saturated NH_4Cl (40 mL). The organic layer was separated and washed with water (30 mL) and brine (30 mL), sequentially. The aqueous layers were combined and extracted with CH_2Cl_2 (2 x 40 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) provided aldehyde **382** (300 mg, 64% yield over 2 steps, R_F = 0.58 in 2:1 hexanes/EtOAc) as a clear oil.

To a solution of NaH (141 mg, 60% dispersion in mineral oil, 3.52 mmol) in THF (9 mL) at 23 °C was added (methyl)triphenylphosphonium bromide (943 mg, 2.64 mmol). The heterogeneous mixture was stirred vigorously for 15 min, and then a solution of aldehyde **382** (300 mg, 1.76 mmol) in THF (2.7 mL) was added dropwise via cannula. The reaction mixture was heated to 65 °C and stirred 8 h. The reaction was then cooled to 0 °C, quenched with saturated NH_4Cl (10 mL), and partitioned between Et_2O (50 mL) and saturated NH_4Cl (35 mL). The aqueous phase was extracted with Et_2O (1 x 40 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (14:1 hexanes/EtOAc eluent) afforded the olefin (134 mg, 45% yield, R_F = 0.49 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of the olefin (134 mg, 0.796 mmol) in wet acetone (7.96 mL, 5% H_2O) at 23 °C was added pyridinium *p*-toluenesulfonate (60.1 mg, 0.239 mmol). The solution was heated to 60 °C and stirred 10 h. Acetone was then removed in vacuo, and the residue was partitioned between Et_2O (35 mL) and saturated $NaHCO_3$ (30 mL). The organic phase was washed with brine (25 mL), dried over $MgSO_4$, and concentrated to an oil, which was used without further purification (R_F = 0.48 in 9:1 hexanes/EtOAc).

Phenylhydrazine (78.3 μl in 0.796 mmol) was dissolved in AcOH (174 μl) at 23 °C, and the solution was heated to 110 °C. A solution of the crude ketone in AcOH (100 μl) was added dropwise, and the resulting mixture was stirred at 110 °C for 72 h. The dark mixture was cooled to 23 °C and diluted with Et_2O. The solution was then partitioned between Et_2O and 5% saturated $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The organic phases were combined, washed with brine, dried over

$MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (4:1 to 2:1 hexanes/CH_2Cl_2 eluent) afforded the annulated indole (56.8 mg, 36% yield over 2 steps, R_F = 0.66 in 1:1 hexanes/CH_2Cl_2) as a pink oil.

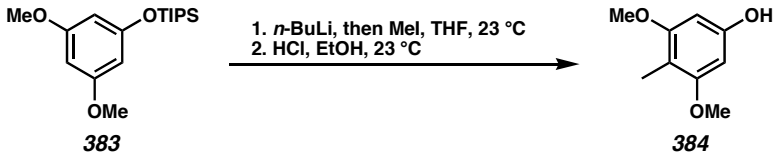
To a solution of the indole (17.9 mg, 0.0907 mmol) in THF (364 μl) at 0 °C was added NaH (7.2 mg, 60% dispersion in mineral oil, 0.181 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (8.5 μl, 0.136 mmol), and allowed to warm to 23 °C. After 15 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (15 mL), and extracted with ether (2 x 20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide the methyl indole (5.6 mg, 29% yield, R_F = 0.48 in 4:1 hexanes/CH_2Cl_2) as a clear oil. This compound matched the product of Table 4.3.3, entry 1 in both TLC and ^{1}H NMR .

4.8 Experimental Section for the Synthesis of Benzofurans and Dihydrobenzofurans

4.8.1 Materials and Methods

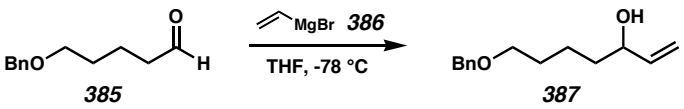
Unless stated otherwise, reactions were conducted in flame-dried glassware under an argon or nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, potassium permanganate, and anisaldehyde staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash column chromatography. Preparative HPLC was performed on a Waters HPLC with an Agilent ZORBAX S1L 4.6 x 250 mm, 5 μm column utilizing a flow rate of 1.5 mL/min and a ramp of 0.11% B/min (A eluent = hexanes, B eluent = EtOAc) with visualization at 270 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass were obtained from the California Institute of Technology Mass Spectral Facility. $Pd(PPh_3)_4$ and $Pd(OAc)_2$ were purchased from Strem Chemicals, Inc., Newburyport, MA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

4.8.2 Preparative Procedures

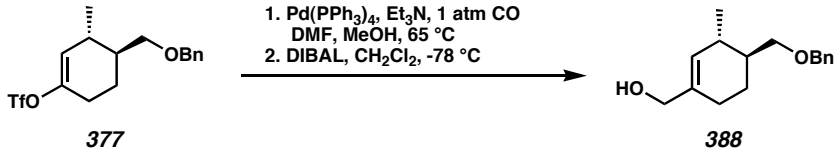


383 ***384***

Phenol 384. To a solution of (3,5-dimethoxyphenoxy)triisopropylsilane[78] (1.36 g, 4.54 mmol) in THF (20.0 mL) was added *n*-BuLi (2.00 mL, 2.50 M in hexanes, 1.10 equiv) dropwise at 23 °C. The resulting mixture was stirred at 23 °C for 1 h and MeI (0.570 mL, 2.00 equiv) was added dropwise. After the addition was complete, the mixture was stirred for an additional 30 min and quenched with saturated aq. NH_4Cl. The mixture was extracted with Et_2O, dried ($MgSO_4$), evaporated, and purified by flash chromatography using 50:1 hexanes/EtOAc to afford (3,5-dimethoxy-4-methyl-phenoxy)triisopropylsilane (1.33 g, 93% yield, R_F = 0.30 in 50:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (s, 2H), 3.76 (s, 6H), 2.01 (s, 3H), 1.22 (m, 3H), 1.12 (d, J = 6.6 Hz, 18H). To a solution of (3,5-dimethoxy-4-methylphenoxy)triisopropylsilane (1.32 g, 4.20 mmol) in 95% EtOH (20.0 mL) was added conc. HCl (1.70 mL). The mixture was stirred at 23 °C for 20 h, concentrated, and extracted with EtOAc. The organic phase was dried ($MgSO_4$), concentrated, and purified by flash chromatography using 2:1 hexanes/EtOAc to afford 3,5-dimethoxy-4-methylphenol (706 mg, 100% yield, R_F = 0.28 in 2:1 hexanes/EtOAc) as a white solid: mp 149-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 2H), 4.96 (br s, 1H), 3.77 (s, 6H), 2.00 (s, 3H).

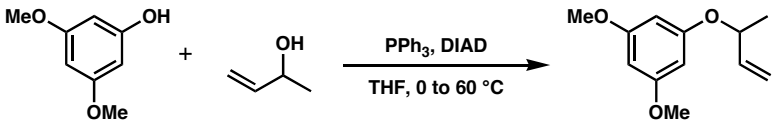


Alcohol 387. To a solution of 5-benzyloxy-1-pentanal[79] (1.65 g, 8.58 mmol) in THF (20.0 mL) at –78 °C was added vinyl magnesium bromide (9.50 mL, 1.00 M in THF, 1.10 equiv) dropwise. After the addition was complete, the reaction was stirred at –78 °C for an additional 30 min. The reaction mixture was quenched with saturated aq. NH_4Cl, extracted with Et_2O, dried ($MgSO_4$), concentrated, and purified by flash chromatography using 3:1 hexanes/EtOAc to afford the alcohol (1.17 g, 62% yield, R_F = 0.27 in 3:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 5.91 (m, 1H), 5.26 (dt, *J* = 1.5, 17.4 Hz, 1H), 5.14 (dt, *J* = 1.5, 10.2, 1H), 4.54 (s, 2H), 4.14 (q, *J* = 6.0 Hz, 1H), 3.52 (t, *J* = 6.6 Hz, 2H), 1.75-1.40 (m, 6H).



Alcohol 388. A flame-dried 25 mL round-bottom flask was sequentially charged with $Pd(PPh_3)_4$ (66.0 mg, 5 mol %), *trans*-4-benzyloxymethyl-3-methylcyclohex-1-enyl triflate (**377**, 400 mg, 1.15 mmol), DMF (10.0 mL), MeOH (2.50 mL), and Et_3N (320 μl, 2.00 equiv). The flask was sealed with a septum and flushed with CO. The mixture was stirred under CO (balloon) at 65 °C for 12 h. The reaction mixture was passed through a plug of celite (0.6 × 5 cm), diluted with ether, and washed with saturated aq. NH_4Cl. The organic phase was dried ($MgSO_4$), concentrated, and purified by flash chromatography using 12:1 hexanes/EtOAc to afford *trans*-4-benzyloxymethyl-3-methyl-cyclohex-1-enecarboxylic acid methyl ester (236 mg, 75% yield, R_F = 0.21 in 12:1 hexanes/EtOAc)

as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.80 (br s, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 3.77 (s, 3H), 3.55 (dd, *J* = 4.2, 9.0 Hz, 1H), 3.40 (dd, *J* = 9.0, 6.6 Hz, 1H), 2.40 (m, 1H), 2.22 (m, 2H), 1.98 (m, 1H), 1.55 (m, 2H), 1.13 (d, *J* = 7.2 Hz, 3H). To a solution of *trans*-4-benzyloxymethyl-3-methyl-cyclohex-1-enecarboxylic acid methyl ester (236 mg, 0.86 mmol) in CH_2Cl_2 (5.00 mL) under N_2 at –78 °C was added DIBAL (353 μl, 2.30 equiv) dropwise. The reaction mixture was stirred at –78 °C for 30 min, quenched with 10% aq. NaOH (2.00 mL), and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), evaporated, and purified by flash chromatography using 2:1 hexanes/EtOAc to afford *trans*-(4-benzyloxymethyl-3-methylcyclohex-1-enyl)methanol (158 mg, 75% yield, R_F = 0.28 in 2:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.50 (br s, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.03 (s, 2H), 3.58 (dd, *J* = 4.2, 9.0 Hz, 1H), 3.39 (dd, *J* = 6.6, 9.0 Hz, 1H), 2.15-1.95 (m, 4H), 1.46 (m, 2H), 1.42 (br s, 1H), 1.06 (d, *J* = 7.2 Hz, 3H).

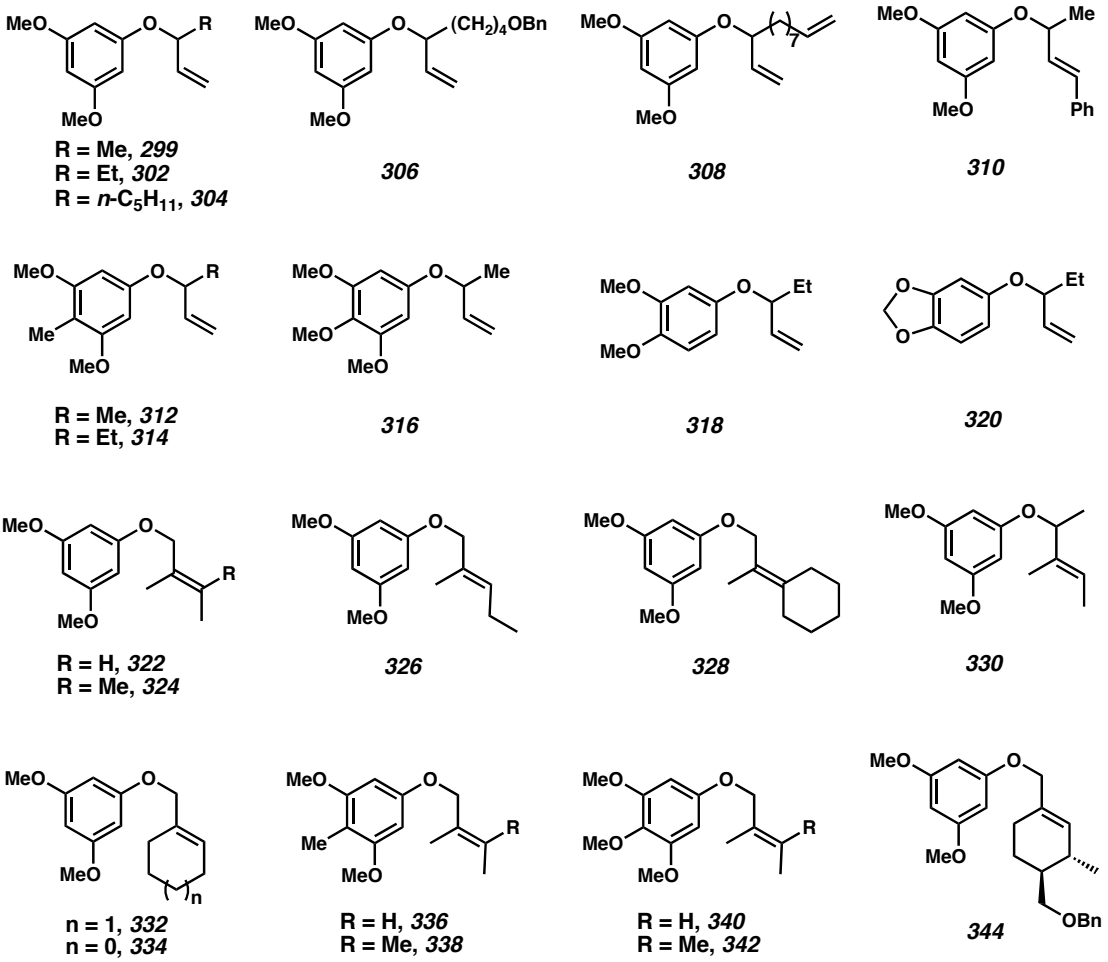


389 ***390*** ***299***

Representative procedure for the preparation of starting substrates. To a 25 mL flame-dried round bottom flask were added 3,5-dimethoxyphenol (308 mg, 2.00 mmol), triphenylphosphine (788 mg, 3.00 mmol), 3-buten-2-ol (216 mg, 3.00 mmol), and THF (10.0 mL). The mixture was stirred until the solids were completely dissolved, and diisopropyl azodicarboxylate (DIAD, 607 mg, 3.00 mmol) was added dropwise at 0 °C. The resulting yellow solution was heated at 60 °C. After the reaction was complete

judged by TLC analysis, the reaction mixture was concentrated in vacuo, triturated with hexanes/EtOAc (20:1), and filtered. The filtrates were concentrated in vacuo, and the residue was purified using hexanes/EtOAc (20:1) by flash chromatography to afford 1,3-dimethoxy-5-(1-methylallyloxy)benzene (287 mg, 69% yield) as a colorless oil.

Substrates for Oxidative Heck Cyclizations



Ether 299. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to the desired product (69% yield, R_F = 0.20 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 1H), 5.90 (m, 1H), 5.30 (m, 1H), 5.20 (m, 1H), 4.80 (m, 1H), 3.79 (s, 6H), 1.46 (d, *J* = 6.3 Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 161.6, 160.1, 139.3, 115.8, 95.0, 93.2, 74.8, 55.5, 21.5; IR (film) 2960, 2839, 1598, 1150 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{12}H_{16}O_3]^+$: 208.1100, found 208.1107.

Ether 302. The compound was prepared using 3,5-dimethoxyphenol and 1-penten-3-ol. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (58% yield, R_F = 0.20 in 20:1 hexanes/EtOAc) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 2.1 Hz, 2H), 6.10 (t, *J* = 2.1 Hz, 1H), 5.87 (m, 1H), 5.26 (m, 2H), 4.52 (m, 1H), 3.79 (s, 6H), 1.79 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 160.3, 137.8, 116.6, 94.8, 93.0, 80.3, 55.3, 28.5, 9.7; IR (film) 2936, 1598, 1205, 1151 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1256.

Ether 304. The compound was prepared using 3,5-dimethoxyphenol and 1-octen-3-ol. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (58% yield, R_F = 0.21 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, *J* = 2.1 Hz, 2H), 6.05 (t, *J* = 2.1 Hz, 1H), 5.82 (m, 1H), 5.25 (d, *J* = 17.4 Hz, 1H), 5.19 (d, *J* = 10.5 Hz, 1H), 4.55 (q, *J* = 6.0 Hz, 1H), 3.73 (s, 6H), 1.82-1.58 (m, 2H), 1.50-1.23 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 160.5, 138.3, 116.5, 95.0, 93.2, 79.3, 55.5, 35.7, 31.9, 25.2, 22.8, 14.3; IR (film) 2932, 1596, 1465, 1152 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{16}H_{24}O_3]^+$: 264.1726, found 264.1731.

Ether 306. The compound was prepared using 3,5-dimethoxyphenol and 7-benzyloxy-1-hepten-3-ol. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford the desired product (48% yield, R_F = 0.25 in 6:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.09 (d, *J* = 1.8 Hz, 2H), 6.05 (t, *J* = 1.8 Hz, 1H), 5.82 (m, 1H), 5.21 (m, 2H), 4.56 (m, 1H), 4.50 (s, 2H), 3.75 (s, 6H), 3.48 (m, 2H), 1.82-1.44 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 160.2, 139.0, 138.0, 128.4, 127.7, 127.5, 116.5, 94.8, 93.0, 78.9, 72.9, 70.2, 55.3, 35.4, 29.6, 22.1; IR (film) 2932, 1595, 1205, 1152 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{22}H_{28}O_4]^+$: 356.1988, found 356.1995.

Ether 308. The compound was prepared using 3,5-dimethoxyphenol and 1,11-dodecadien-3-ol.[80] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (50% yield, R_F = 0.27 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10-6.05 (m, 3H), 5.86-5.76 (m, 2H), 5.28-5.18 (m, 2H), 5.03-4.91 (m, 2H), 4.55 (q, *J* = 6.6 Hz, 1H), 3.75 (s, 6H), 2.10-2.00 (m, 2H), 1.82-1.54 (m, 2H), 1.50-1.20 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 160.5, 139.4, 138.3, 116.5, 114.4, 95.0, 93.1, 79.3, 55.5, 35.8, 34.0, 29.6, 29.4, 29.3, 29.1, 25.5; IR (film) 2932, 2855, 1560, 1157 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{20}H_{30}O_3]^+$: 318.2195, found 318.2209.

Ether 310. The compound was prepared using 3,5-dimethoxyphenol and (*E*)-4-phenyl-3-buten-2-ol.[81] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (58% yield, R_F = 0.20 in 20:1 hexanes/EtOAc) as a pale yellow

oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 5H), 6.65 (d, *J* = 16.5 Hz, 1H), 6.30 (dd, *J* = 6.3, 16.5 Hz, 1H), 6.23-6.10 (m, 3H), 4.98 (m, 1H), 3.79 (s, 6H), 1.56 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 159.9, 136.5, 130.7, 130.6, 128.5, 127.7, 126.5, 94.9, 93.2, 74.6, 55.3, 21.7; IR (film) 2980, 2836, 1595, 1190, 1148 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{18}H_{20}O_3]^+$: 284.1413, found 284.1424.

Ether 312. The compound was prepared using 3,5-dimethoxy-4-methylphenol and 3-buten-2-ol. The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (41% yield, R_F = 0.25 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (s, 2H), 5.93 (m, 1H), 5.29 (d, *J* = 17.4 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 4.78 (quintet, *J* = 6.3 Hz, 1H), 3.78 (s, 6H), 2.01 (s, 3H), 1.44 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 157.4, 148.9, 139.8, 115.7, 93.0, 75.2, 55.9, 21.6, 7.9; IR (film) 2922, 1560, 1459, 1143 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1246.

Ether 314. The compound was prepared using 3,5-dimethoxy-4-methylphenol and 1-penten-3-ol. The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (34% yield, R_F = 0.20 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (s, 2H), 5.90 (m, 1H), 5.32 (d, *J* = 18.9 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 4.53 (m, 1H), 3.82 (s, 6H), 2.04 (s, 3H), 1.80 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 157.7, 138.3, 116.5, 106.8, 92.7, 80.6, 55.7, 28.6, 9.7, 7.7; IR (film) 2940, 1605, 1454, 1133 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1413.

Ether 316. The compound was prepared using 3,4,5-trimethoxyphenol and 3-buten-2-ol. The reaction mixture was chromatographed using 8:1 hexanes/EtOAc to afford the desired product (51% yield, R_F = 0.25 in 8:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (s, 2H), 5.89 (m, 1H), 5.26 (dt, *J* = 1.2, 17.1 Hz, 1H), 5.16 (dt, *J* = 1.2, 10.5 Hz, 1H), 4.71 (quintet, *J* = 6.3 Hz, 1H), 3.79 (s, 6H), 3.76 (s, 3H), 1.40 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 153.8, 139.6, 132.2, 115.8, 94.1, 75.5, 61.2, 56.2, 21.5; IR (film) 2940, 1594, 1234, 1135 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{18}O_4]^+$: 238.1205, found 238.1205.

Ether 318. The compound was prepared using 3,4-dimethoxyphenol and 1-penten-3-ol. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford the desired product (34% yield, R_F = 0.27 in 6:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, J = 9.0 Hz, 1H), 6.61 (d, *J* = 3.0 Hz, 1H), 6.48 (dd, *J* = 3.0, 9.0 Hz, 1H), 5.90 (m, 1H), 5.25 (m, 2H), 4.48 (q, *J* = 7.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 1.80 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 138.2, 116.6, 111.7, 106.2, 102.3, 101.2, 81.2, 56.4, 55.8, 28.5, 9.7; IR (film) 2965, 1596, 1509, 1229 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1255.

Ether 320. The compound was prepared using 3,4-methylenedioxyphenol and 1-penten-3-ol. The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (56% yield, R_F = 0.22 in 25:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 6.39 (dd, *J*

= 2.1, 8.4 Hz, 1H), 5.93 (s, 2H), 5.83 (m, 1H), 5.25 (m, 2H), 4.40 (q, *J* = 7.2 Hz, 1H), 1.77 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 148.0, 141.6, 138.0, 116.6, 108.2, 107.9, 101.1, 99.6, 81.9, 28.5, 9.7; IR (film) 2969, 2879, 1630, 1486, 1189 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{14}O_3]^+$: 206.0943, found 206.0941.

Ether 322. The compound was prepared using 3,5-dimethoxyphenol and (*E*)-2-methyl-2-buten-1-ol.[82] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (77% yield, R_F = 0.30 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, *J* = 1.8 Hz, 2H), 6.08 (t, *J* = 1.8 Hz, 1H), 5.63 (q, *J* = 6.6 Hz, 1H), 4.34 (s, 2H), 3.76 (s, 6H), 2.17 (s, 3H), 1.73 (s, 3H), 1.67 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 160.9, 131.7, 123.6, 93.7, 93.0, 74.2, 55.3, 13.7, 13.3; IR (film) 2924, 1594, 1207, 1153 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1248.

Ether 324. The compound was prepared using 3,5-dimethoxyphenol and 2,3-dimethyl-2-buten-1-ol.[83] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (44% yield, R_F = 0.25 in 20:1 hexanes/EtOAc) as a colorless oil. Also the compound was prepared as follows: To a flame-dried vial were added 3,5-dimethoxyphenol (308 mg, 2.00 mmol), 1-bromo-2,3-dimethyl-2-butene[84] (489 mg, 3.00 mmol), Cs_2CO_3 (978 mg, 3.00 mmol), and acetone (6.00 mL). The mixture was sealed and heated at 75 °C for 10 h. The mixture was cooled, filtered, concentrated, and chromatographed using 20:1 hexanes/EtOAc to afford the desired product (68% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, *J* = 2.4 Hz, 2H), 6.12 (t, *J* = 2.4

Hz, 1H), 4.49 (s, 2H), 3.80 (s, 6H), 1.82 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.2, 131.3, 123.8, 93.5, 93.0, 69.3, 55.3, 21.0, 20.3, 16.8; IR (film) 2997, 2935, 1601, 1474, 1151 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1405.

Ether 326. The compound was prepared using 3,5-dimethoxyphenol and (*E*)-2-methyl-2-peten-1-ol.[85] The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (67% yield, R_F = 0.20 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 5.59 (t, *J* = 6.6 Hz, 1H), 4.38 (s, 2H), 3.80 (s, 6H), 2.13 (m, 2H), 1.77 (s, 3H), 1.03 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.0, 131.1, 130.3, 93.7, 93.0, 74.3, 55.3, 21.0, 13.9, 13.8; IR (film) 2953, 1597, 1461, 1199, 1150 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1415.

Ether 328. The compound was prepared using 3,5-dimethoxyphenol and 2-cyclohexylidene-1-propanol.[86] The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (66% yield, R_F = 0.21 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 4.50 (s, 2H), 3.80 (s, 6H), 2.29 (m, 4H), 1.84 (s, 3H), 1.60 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.2, 139.7, 120.4, 93.6, 93.0, 68.8, 55.3, 30.9, 30.5, 28.3, 27.8, 26.8, 16.4; IR (film) 2917, 1592, 1199, 1150 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{17}H_{24}O_3]^+$: 276.1726, found 276.1717.

Ether 330. The compound was prepared using 3,5-dimethoxyphenol and (*E*)-3-methyl-3-penten-2-ol.[87] The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (43% yield, R_F = 0.21 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (d, *J* = 2.1 Hz, 1H), 6.09 (t, *J* = 2.1 Hz, 1H), 5.59 (m, 1H), 4.66 (q, *J* = 6.6 Hz, 1H), 3.78 (s, 6H), 1.65 (m, 6H), 1.43 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 160.1, 136.3, 121.0, 94.7, 92.8, 79.1, 55.3, 20.5, 13.1, 11.0; IR (film) 2935, 1599, 1205, 1153 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1418.

Ether 332. The compound was prepared using 3,5-dimethoxyphenol and 1-cyclohexene-1-methanol.[88] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (73% yield, R_F = 0.25 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 5.85 (br s, 1H), 4.35 (s, 2H), 3.80 (s, 6H), 2.12 (m, 4H), 1.80-1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.0, 133.8, 125.9, 93.7, 93.0, 72.9, 55.3, 25.9, 25.1, 22.5, 22.3; IR (film) 2931, 2838, 1600, 1152 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{15}H_{20}O_3]^+$: 248.1413, found 248.1404.

Ether 334. The compound was prepared using 3,5-dimethoxyphenol and 1-cyclopentene-1-methanol.[89] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (67% yield, R_F = 0.28 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 5.79 (br s, 1H), 4.57 (s, 2H), 3.80 (s, 6H), 2.43 (m, 4H),

1.98 (quintet, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 160.9, 140.4, 128.4, 93.6, 93.0, 67.2, 55.3, 32.9, 32.5, 23.3; IR (film) 2952, 1599, 1205, 1152 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1246.

Ether 336. The compound was prepared using 3,5-dimethoxy-4-methylphenol and (*E*)-2-methyl-2-buten-1-ol.[82] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (49% yield, R_F = 0.25 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (s, 2H), 5.70 (q, J = 6.6 Hz, 1H), 4.41 (s, 2H), 3.83 (s, 6H), 2.05 (s, 3H), 1.79 (s, 3H), 1.71 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 158.3, 132.0, 123.6, 106.7, 91.4, 74.4, 55.7, 13.7, 13.3, 7.7; IR (film) 2936, 1611, 1195, 1141 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1421.

Ether 338. The compound was prepared using 3,5-dimethoxy-4-methylphenol and 2,3-dimethyl-2-buten-1-ol.[83] The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (52% yield, R_F = 0.26 in 25:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 2H), 4.53 (s, 2H), 3.84 (s, 6H), 2.06 (s, 3H), 1.84 (s, 6H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 158.6, 131.1, 124.0, 106.6, 91.3, 69.3, 55.7, 21.0, 20.3, 16.8, 7.7; IR (film) 2935, 1611, 1459, 1195, 1142 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{15}H_{22}O_3]^+$: 250.1569, found 250.1571.

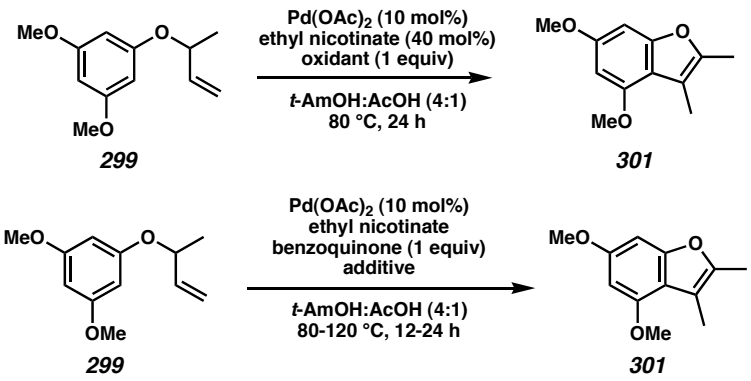
Ether 340. The compound was prepared using 3,4,5-trimethoxyphenol and (*E*)-2-methyl-2-buten-1-ol.[82] The reaction mixture was chromatographed using 7:1 hexanes/EtOAc to afford the desired product (57% yield, R_F = 0.25 in 7:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (s, 2H), 5.64 (q, *J* = 6.6 Hz, 1H), 4.34 (s, 2H), 3.83 (s, 6H), 3.78 (s, 3H), 2.16 (s, 3H), 1.74 (s, 3H), 1.67 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 15.6, 132.3, 131.8, 123.8, 92.5, 74.6, 61.0, 56.1, 13.7, 13.3; IR (film) 2938, 1593, 1506, 1225, 1130 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{14}H_{20}O_4]^+$: 252.1362, found 252.1352.

Ether 342. To a flame-dried vial were added 3,4,5-trimethoxyphenol (368 mg, 2.00 mmol), 1-bromo-2,3-dimethyl-2-butene (489 mg, 3.00 mmol), Cs_2CO_3 (978 mg, 3.00 mmol), and acetone (6.00 mL). The mixture was sealed and heated at 75 °C for 10 h. The mixture was cooled, filtered, concentrated, and chromatographed using 5:1 hexanes/EtOAc to afford the desired product (65% yield, R_F = 0.30 in 5:1 hexanes/EtOAc) as a white solid: mp 60-61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 2H), 4.50 (s, 2H), 3.87 (s, 6H), 3.82 (s, 3H), 1.83 (s, 6H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 153.7, 132.2, 131.3, 123.8, 92.4, 69.5, 61.1, 56.1, 21.0, 20.3, 16.8; IR (film) 2936, 1593, 1505, 1226, 1129 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{15}H_{22}O_4]^+$: 266.1518, found 266.1518.

Ether 344. The compound was prepared using 3,5-dimethoxyphenol and *trans*-(4-benzyloxymethyl-3-methylcyclohex-1-enyl)methanol. The reaction mixture was chromatographed using 12:1 hexanes/EtOAc to afford the desired product (63% yield, R_F

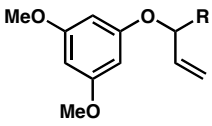
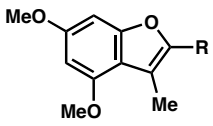
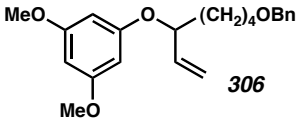
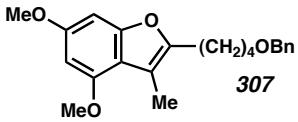
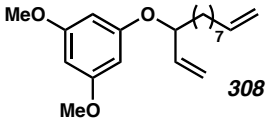
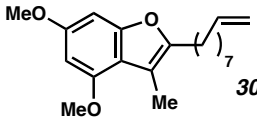
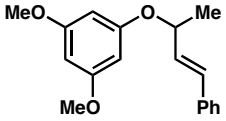
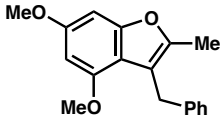
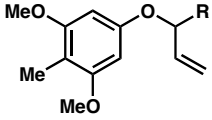
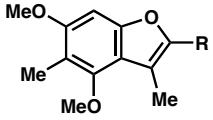
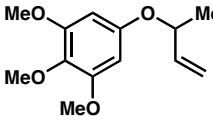
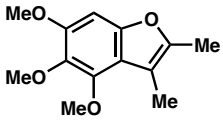
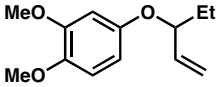
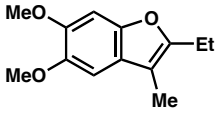
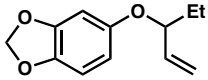
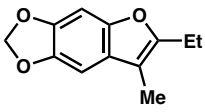
= 0.28 in 12:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.14 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 5.63 (br s, 1H), 4.55 (m, 2H), 4.37 (s, 2H), 3.80 (s, 6H), 3.58 (m, 1H), 3.40 (m, 1H), 2.15-1.95 (m, 4H), 1.56 (m, 2H), 1.07 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 161.0, 138.8, 132.8, 131.2, 128.4, 127.5, 127.5, 93.7, 93.1, 73.3, 73.1, 72.5, 55.3, 40.9, 32.2, 24.9, 20.3, 15.3; IR (film) 2927, 2870, 1600, 1153 cm^{-1}; HRMS (FAB^{+}) *m/z* calc'd for $[C_{24}H_{30}O_4]^{+}$: 382.2144, found 382.2146.

4.8.3 Palladium-Catalyzed Benzofuran and Dihydrobenzofuran Synthesis



Representative procedure for optimization (Tables 4.4.1 and 4.4.2): A flame-dried 1-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (2.3 mg, 0.0100 mmol), followed by ethyl nicotinate (0-40 mol%), tridecane (12.0 μl, 0.049 mmol, internal standard), **299** (20.8 mg, 0.100 mmol), NaOAc (1 equiv or 20 mol%), and a mixture of *t*-amyl alcohol and acetic acid (1.0 mL, 4:1 v/v). The resulting mixture was stirred at 23 °C for 2 min, and then oxidant (1 equiv) was added. The reaction mixture was heated at 100 °C for 12 h. The reaction mixture was then cooled, filtered through a short plug of silica gel (Et_2O as eluent), and analyzed by GC.

Table 4.4.3 (reproduced) The palladium(II)-catalyzed oxidative benzofuran synthesis.[a]

entry	substrate	product	time (h)	% yield[b]
1	 R = Me ***299***	 R = Me ***301***	12	77
2	R = Et ***302***	R = Et ***303***	12	74
3	R = *n*-C_5H_{11} ***304***	R = *n*-C_5H_{11} ***305***	13	72
4	 ***306***	 ***307***	12	62
5	 ***308***	 ***309***	14	54
6	 ***310***	 ***311***	12	61
7	 R = Me ***312***	 R = Me ***313***	14	75
8	R = Et ***314***	R = Et ***315***	12	79
9	 ***316***	 ***317***	12	61
10	 ***318***	 ***319***	16	56[c]
11	 ***320***	 ***321***	16	52[c]

[a] 10 mol% $Pd(OAc)_2$, 20 mol% ethyl nicotinate, 20 mol% NaOAc, 1 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C. [b] Isolated yield. [c] Produced as a single regioisomer.

Representative procedure for the Pd-catalyzed synthesis of benzofurans: (Table 4.4.3): A flame-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (11.3 mg, 0.0500 mmol), followed by ethyl nicotinate (13.8 μl, 0.100 mmol), **299** (104.1 mg, 0.500 mmol), NaOAc (8.2 mg, 0.100 mmol), and a mixture of *t*-amyl alcohol and acetic acid (5.00 mL, 4:1 v/v). The resulting mixture was stirred at 23 °C for 2 min, and then benzoquinone (54.1 mg, 0.500 mmol) was added. The reaction mixture

was heated at 100 °C for 12 h. The reaction mixture was then cooled, filtered through a short plug of silica gel (0.6 × 5 cm, Et_2O as eluent), evaporated, and purified by flash chromatography on a silica gel column.

Benzofuran 301. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (79 mg, 77% yield, R_F = 0.26 in 20:1 hexanes/EtOAc) as a white sold: mp 53-54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (d, *J* = 2.1 Hz, 1H), 6.29 (d, *J* = 2.1 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 155.5, 154.4, 147.6, 113.2, 109.5, 93.5, 88.0, 55.7, 55.4, 11.4, 9.8; IR (film) 2917, 1602, 1427, 1108 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{14}O_3]^+$: 206.0943, found 206.0939.

Benzofuran 303. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (81 mg, 74% yield, R_F = 0.26 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (d, *J* = 2.1 Hz, 1H), 6.30 (d, *J* = 2.1 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.71 (q, *J* = 7.5 Hz, 2H), 2.29 (s, 3H), 1.29 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 155.5, 154.5, 152.8, 113.2, 108.6, 93.5, 88.0, 55.7, 55.4, 19.3, 13.0, 9.6; IR (film) 2969, 1603, 1501, 1208, 1149 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1100, found 220.1110.

Benzofuran 305. The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (95 mg, 72% yield, R_F = 0.30 in 25:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (d, *J* = 2.1 Hz, 1H), 6.26 (d, *J* = 2.1

Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.63 (t, J = 7.2 Hz, 2H), 2.25 (s, 3H), 1.66 (quintet, J = 7.2 Hz, 2H), 1.31 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 155.8, 154.7, 152.0, 113.4, 109.5, 93.7, 88.2, 55.9, 55.6, 31.5, 28.4, 26.0, 22.7, 14.2, 9.9; IR (film) 2930, 1603, 1501, 1148, 1113 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{16}H_{22}O_3]^+$: 262.1569, found 262.1570.

Benzofuran 307. The reaction was carried out in 0.40 mmol scale and chromatographed using 10:1 hexanes/EtOAc to afford the desired product (88 mg, 62% yield, R_F = 0.32 in 10:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5H), 6.60 (d, J = 1.8 Hz, 1H), 6.32 (d, J = 1.8 Hz, 1H), 4.55 (s, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.54 (t, J = 6.6 Hz, 3H), 2.73 (t, J = 6.6 Hz, 2H), 2.30 (s, 3H), 1.84-1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 155.6, 154.5, 151.3, 138.7, 128.4, 127.7, 127.5, 113.2, 109.6, 93.6, 88.0, 73.0, 70.1, 55.7, 55.4, 29.2, 25.6, 25.2, 9.8; IR (film) 2939, 2860, 1602, 1500, 1202 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{22}H_{26}O_4]^+$: 354.1831, found 354.1824.

Benzofuran 309. The reaction mixture was chromatographed using 2:1 hexanes/$CHCl_3$ to afford the desired product (86 mg, 54% yield, R_F = 0.25 in 2:1 hexanes/$CHCl_3$) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (d, J = 2.1 Hz, 1H), 6.26 (d, J = 2.1 Hz, 1H), 5.81 (m, 1H), 5.02-4.91 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.63 (t, J = 7.2 Hz, 2H), 2.24 (s, 3H), 2.04 (m, 2H), 1.65 (m, 2H), 1.32 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 155.8, 154.7, 151.9, 139.4, 114.4, 113.4, 109.5, 93.7, 88.2, 55.9, 55.6, 34.0, 29.5, 29.3, 29.1, 28.6, 26.1, 10.0; IR (film) 2927, 2854, 1602, 1148 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{20}H_{28}O_3]^+$: 316.2039, found 216.2040.

Benzofuran 311. The reaction mixture was chromatographed using 3:1 hexanes/$CHCl_3$ to afford the desired product (86 mg, 61% yield, R_F = 0.26 in 3:1 hexanes/$CHCl_3$) as a white solid: mp 72-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.15 (m, 5H), 6.60 (d, *J* = 2.1 Hz, 1H), 6.28 (d, *J* = 2.1 Hz, 1H), 4.09 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 155.7, 154.1, 148.9, 141.6, 128.3, 128.2, 125.7, 113.0, 112.6, 93.8, 88.0, 55.7, 55.2, 30.2, 11.9; IR (film) 2917, 1603, 1501, 1217, 1148 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{18}H_{18}O_3]^+$: 282.1256, found 282.1252.

Benzofuran 313. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (83 mg, 75% yield, R_F = 0.31 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 153.7, 151.7, 148.3, 116.2, 113.9, 108.4, 90.4, 62.0, 55.9, 11.5, 9.3, 8.6; IR (film) 2942, 1593, 1223, 1149 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1100, found 220.1107.

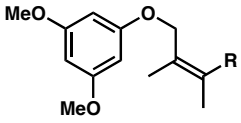
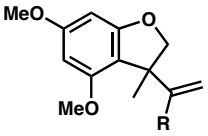
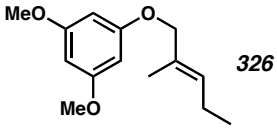
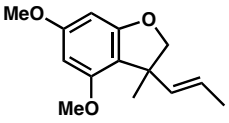
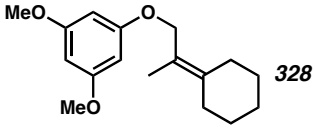
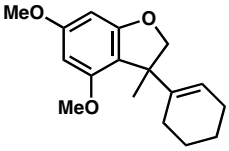
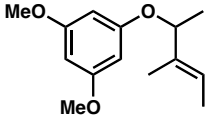
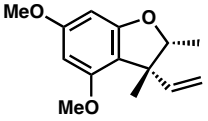
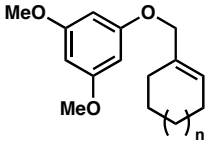
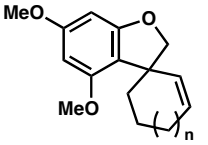
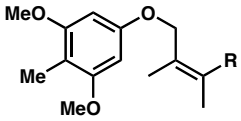
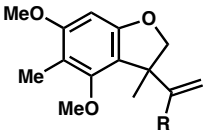
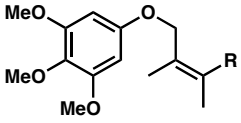
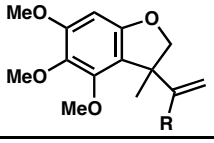
Benzofuran 315. The reaction mixture was chromatographed using 4:1 hexanes/$CHCl_3$ to afford the desired product (93 mg, 79% yield, R_F = 0.25 in 4:1 hexanes/$CHCl_3$) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.72 (q, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 2.24 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 153.7, 153.5, 151.9, 116.3, 113.9, 107.5, 90.5, 62.0, 55.9, 19.4, 12.9, 9.2, 8.6; IR (film) 2938, 1594, 1461, 1149 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1248.

Benzofuran 317. The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford the desired product (72 mg, 61% yield, R_F = 0.29 in 10:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 1H), 3.96 (s, 3H), 3.86 (s, 6H), 2.29 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 150.5, 148.8, 146.5, 138.2, 116.5, 109.3, 91.1, 61.8, 61.3, 56.3, 11.5, 9.3; IR (film) 2937, 1620, 1468, 1199 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_4]^+$: 236.1049, found 236.1051.

Benzofuran 319. The reaction mixture was chromatographed using 2:3 hexanes/$CHCl_3$ to afford the desired product (62 mg, 56% yield, R_F = 0.25 in 2:3 hexanes/$CHCl_3$) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.89 (s, 1H), 3.96 (s, 3H), 3.94 (s, 6H), 2.74 (q, *J* = 7.5 Hz, 2H), 2.16 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 148.1, 147.0, 146.0, 122.3, 108.7, 100.7, 95.3, 56.5, 56.3, 19.8, 12.9, 7.9; IR (film) 2938, 1621, 1489, 1212 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1100, found 220.1103.

Benzofuran 321. The reaction mixture was chromatographed using 5:1 hexanes/$CHCl_3$ to afford the desired product (53 mg, 52% yield, R_F = 0.29 in 5:1 hexanes/$CHCl_3$) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.83 (s, 1H), 5.98 (s, 3H), 2.73 (q, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 148.6, 145.0, 143.8, 123.8, 109.0, 101.0, 97.6, 93.2, 19.8, 12.9, 7.9; IR (film) 2973, 1463, 1292, 1170 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{12}O_3]^+$: 204.0787, found 204.0795.

Table 4.4.4 (reproduced) The palladium(II)-catalyzed oxidative dihydrobenzofuran synthesis.

entry	substrate	product	time (h)	% yield[b]
1	 R = H ***322***	 R = H ***323***	16	74
2[c]	R = Me ***324***	R = Me ***325***	12	71
3	 ***326***	 ***327***	30	58[d]
4	 ***328***	 ***329***	28	55
5	 ***330***	 ***331***	15	74[e]
6	 n = 1 ***332***	 n = 1 ***333***	24	80
7	n = 0 ***334***	n = 0 ***335***	18	78
8	 R = H ***336***	 R = H ***337***	15	50
9	R = Me ***338***	R = Me ***339***	15	63
10	 R = H ***340***	 R = H ***341***	15	60
11	R = Me ***342***	R = Me ***343***	15	66

[a] 10 mol% $Pd(OAc)_2$, 20 mol% ethyl nicotinate, 20 mol% NaOAc, 1 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C. [b] Isolated yield. c Performed with 5 mol% $Pd(OAc)_2$ and 10 mol% ethyl nicotinate. [d] An inseparable mixture of roughly 66% product (*E*/*Z* = 3:1) and 10% starting material was isolated after 18 h. This mixture was subjected to another reaction with 5 mol% $Pd(OAc)_2$, 10 mol% ethyl nicotinate, 20 mol% NaOAc, and 50 mol% benzoquinone for 12 h, after which only the *E* isomer was observed. The yield presented is the overall yield of isolated product. [e] A 2.3:1 mixture of diastereomers was isolated with the major isomer shown.

Representative procedure for the Pd-catalyzed synthesis of dihydrobenzofurans (Table 4.4.4): A flame-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (11.3 mg, 0.0500 mmol), followed by ethyl nicotinate (13.8 μl, 0.100 mmol), **322** (111 mg, 0.500 mmol), NaOAc (8.2 mg, 0.100 mmol), and a mixture of *t*-amyl alcohol and acetic acid (5.00 mL, 4:1 v/v). The resulting mixture was stirred at 23 °C for 2 min, and then benzoquinone (54.1 mg, 0.500 mmol) was added. The reaction mixture was heated at 100 °C for 12 h. The reaction mixture was then cooled, filtered through a short plug of silica gel (0.6 × 5 cm, Et_2O as eluent), evaporated, and purified by flash chromatography on a silica gel column.

Dihydrobenzofuran 323. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (81 mg, 74% yield, R_F = 0.24 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17-6.05 (m, 3H), 5.09-4.98 (m, 2H), 4.44 (d, *J* = 9.0 Hz, 1H), 4.22 (d, *J* = 9.0 Hz, 1H), 3.80 (s, 6H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.6, 157.4, 142.9, 112.1, 91.7, 88.6, 83.6, 55.5, 55.3, 48.1, 23.2; IR (film) 2961, 1601, 1500, 1151, 1098 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1100, found 220.1098.

Dihydrobenzofuran 325. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc and further purified by preparative HPLC to afford the desired product (83 mg, 71% yield, R_F = 0.26 in 20:1 hexanes/EtOAc) as a colorless oil: . ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, *J* = 2.1 Hz, 1H), 6.04 (d, *J* = 2.1 Hz, 1H), 4.88 (s, 1H), 4.81 (s, 1H), 4.43 (d, *J* = 8.7 Hz, 1H), 4.18 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 1.74 (s,

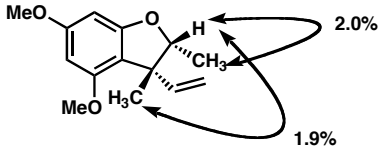
3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.8, 157.3, 148.2, 112.5, 110.3, 91.5, 88.4, 83.6, 55.5, 55.3, 50.6, 23.4, 20.2; IR (film) 2964, 1601, 1500, 1201, 1151 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1267.

Dihydrobenzofuran 327. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (68 mg, 58% yield, R_F = 0.25 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, *J* = 2.1 Hz, 1H), 6.02 (d, *J* = 2.1 Hz, 1H), 5.69 (dq, *J* = 1.8, 15.3 Hz, 1H), 5.36 (dq, *J* = 6.3, 15.3 Hz, 1H), 4.37 (d, *J* = 8.4 Hz, 1H), 4.16 (d, *J* = 8.4 Hz, 1H), 3.76 (s, 6H), 1.67 (dd, *J* = 1.5, 6.3 Hz, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.7, 157.6, 136.1, 123.0, 113.0, 91.9, 88.8, 84.4, 55.7, 55.5, 47.6, 24.1, 18.2; IR (film) 2960, 1604, 1499, 1150, 1095 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1245.

Dihydrobenzofuran 329. The reaction mixture was chromatographed using 30:1 hexanes/EtOAc and further purified by preparative HPLC to afford the desired product (60 mg, 55% yield, R_F = 0.22 in 30:1 hexanes/EtOAc) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, *J* = 2.1 Hz, 1H), 6.04 (d, *J* = 2.1 Hz, 1H), 5.48 (m, 1H), 4.38 (d, *J* = 8.7 Hz, 1H), 4.14 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.08-1.55 (m, 8H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.6, 157.3, 139.8, 120.6, 112.9, 91.5, 88.4, 83.8, 55.5, 55.3, 50.6, 25.6, 25.5, 23.3, 23.1, 22.4; IR (film) 2931, 1622, 1150, 1097 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{17}H_{22}O_3]^+$: 274.1569, found 274.1580.

Dihydrobenzofuran 331. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired products (81 mg, 74% yield, R_F = 0.28 in 20:1 hexanes/EtOAc) in a 2.3:1 ratio as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) major isomer: δ 6.07 (m, 3H), 5.80 (dd, *J* = 10.5, 17.4 Hz, 1H), 5.12 (m, 2H), 4.42 (q, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 1.52 (s, 3H), 1.34 (d, *J* = 6.6 Hz, 3H); minor isomer: δ 4.80 (dd, *J* = 1.5, 17.4 Hz, 2H), 4.55 (q, *J* = 6.6 Hz, 1H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.27 (s, 3H), other peaks overlapped with peaks of major isomer; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 161.6, 161.0, 160.5, 157.7, 157.0, 143.2, 139.5, 114.2, 112.7, 112.3, 91.7, 91.7, 90.1, 88.6, 88.5, 88.5, 87.6, 55.5, 55.3, 55.3, 50.2, 49.9, 22.1, 17.5, 14.9, 14.0; IR (film) 2970, 1606, 1500, 1148 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1258.

Figure 4.8.1 NOE measurements of dihydrobenzofuran **331**.



Dihydrobenzofuran 333. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc and recrystallized from hexanes to afford the desired product (99 mg, 80% yield, R_F = 0.30 in 20:1 hexanes/EtOAc) as a white solid: mp 80-81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, *J* = 2.1 Hz, 1H), 6.05 (d, *J* = 2.1 Hz, 1H), 5.85 (m, 1H), 5.70 (m, 1H), 4.36 (d, *J* = 8.7 Hz, 1H), 4.21 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.20-2.00 (m, 3H), 1.83 (m, 2H), 1.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.7, 157.4, 131.2, 127.7, 113.5, 91.7, 88.5, 82.6, 55.5, 55.4, 46.5, 32.5, 24.4, 20.1; IR

(film) 2934, 1603, 1200, 1146 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{15}H_{18}O_3]^+$: 246.1256, found 246.1252.

Dihydrobenzofuran 335. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc and recrystallized from hexanes to afford the desired product (91 mg, 78% yield, R_F = 0.28 in 20:1 hexanes/EtOAc) as a white solid: mp 49-50 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, *J* = 2.1 Hz, 1H), 6.07 (d, *J* = 2.1 Hz, 1H), 5.83 (m, 1H), 5.67 (m, 1H), 4.35 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.65-2.55 (m, 1H), 2.50-2.35 (m, 2H), 1.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 161.7, 157.4, 134.4, 130.9, 112.3, 91.7, 88.4, 83.2, 55.6, 55.4, 45.0, 36.0, 32.0; IR (film) 2938, 1602, 1145, 1095 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{16}O_3]^+$: 232.1100, found 232.1091.

Dihydrobenzofuran 337. The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford the desired product (59 mg, 50% yield, R_F = 0.20 in 40:1 hexanes/EtOAc) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 1H), 6.15 (dd, *J* = 10.5, 16.8 Hz, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 5.09 (d, *J* = 16.8 Hz, 1H), 4.38 (d, *J* = 8.4 Hz, 1H), 4.19 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.09 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 159.1, 156.1, 143.5, 117.2, 112.4, 111.7, 90.3, 83.5, 61.3, 55.8, 48.4, 23.0, 8.8; IR (film) 2939, 1614, 1471, 1134, 1072 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1250.

Dihydrobenzofuran 339. The reaction mixture was chromatographed using 1:1 hexanes/$CHCl_3$ to afford the desired product (78 mg, 63% yield, R_F = 0.25 in 1:1

hexanes/$CHCl_3$) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (s, 1H), 4.92 (s, 1H), 4.88 (s, 1H), 4.43 (d, *J* = 8.4 Hz, 1H), 4.16 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 2.09 (s, 3H), 1.75 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 155.9, 148.9, 117.2, 111.5, 110.5, 90.0, 83.3, 60.7, 55.7, 50.8, 23.8, 20.0, 8.8; IR (film) 2940, 1614, 1471, 1130 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{15}H_{20}O_3]^+$: 248.1413, found 248.1416.

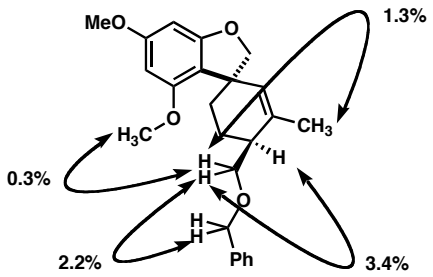
Dihydrobenzofuran 341. The reaction mixture was chromatographed using 8:1 hexanes/EtOAc to afford the desired product (72 mg, 60% yield, R_F = 0.30 in 8:1 hexanes/EtOAc) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (s, 1H), 6.13 (dd, *J* = 10.5, 17.4 Hz, 1H), 5.12 (dd, *J* = 0.9, 10.5 Hz, 1H), 5.05 (dd, *J* = 0.9, 17.4 Hz, 1H), 4.39 (d, *J* = 8.4 Hz, 1H), 4.19 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 154.3, 150.7, 143.1, 136.2, 116.9, 112.4, 90.6, 83.5, 61.0, 60.9, 56.1, 48.8, 23.4; IR (film) 2937, 1614, 1472, 1197, 1105 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{14}H_{18}O_4]^+$: 250.1205, found 250.1207.

Dihydrobenzofuran 343. The reaction mixture was chromatographed using 8:1 hexanes/EtOAc to afford the desired product (87 mg, 66% yield, R_F = 0.30 in 8:1 hexanes/EtOAc) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.86 (s, 1H), 4.78 (s, 1H), 4.37 (d, *J* = 8.4 Hz, 1H), 4.11 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 1.70 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 154.3, 150.6, 148.5, 136.1, 117.1, 110.7, 90.5, 83.5, 61.2, 60.9, 56.4, 51.6, 24.1, 20.4; IR

(film) 2939, 1614, 1472, 1199, 1103 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{15}H_{20}O_4]^+$: 264.1362, found 264.1364.

Dihydrobenzofuran 346. The reaction was carried out in a 0.34 mmol scale, and the crude material was chromatographed using 12:1 hexanes/EtOAc and recrystallized from hexanes/EtOAc (to remove a small amount of the starting material) to afford the desired product (78 mg, 60% yield, R_F = 0.29 in 12:1 hexanes/EtOAc) as a white solid: mp 99-100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 6.06 (d, *J* = 2.1 Hz, 1H), 5.99 (d, *J* = 2.1 Hz, 1H), 5.43 (s, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 8.4 Hz, 1H), 4.17 (d, *J* = 8.4 Hz, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.58 (m, 2H), 2.35 (m, 1H), 2.09 (m, 2H), 1.78 (s, 3H), 1.60 (m, 2H); ^{1}H NMR (300 MHz, C_6D_6) δ 7.34-7.30 (m, 2H), 7.20-7.04 (m, 3H), 6.26 (d, *J* = 2.1 Hz, 1H), 6.06 (d, *J* = 2.1 Hz, 1H), 5.45 (q, *J* = 1.2 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 9.0 Hz, 1H), 4.14 (dd, *J* = 1.2, 9.0 Hz, 1H), 3.60 (m, 2H), 3.31 (s, 3H), 3.19 (s, 3H), 2.34-2.22 (m, 2H), 2.16-2.06 (m, 1H), 1.68-1.60 (m, 4H), 1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 161.7, 157.2, 138.7, 134.4, 128.4, 128.1, 127.6, 127.5, 113.5, 91.7, 88.5, 83.1, 73.0, 70.4, 55.5, 55.2, 46.8, 38.6, 27.7, 23.0, 22.5; IR (film) 2937, 1605, 1499, 1147, 1098 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{24}H_{28}O_4]^+$: 380.1988, found 380.1981.

Figure 4.8.2 NOE measurements of dihydrobenzofuran **346 (**in C_6D_6).



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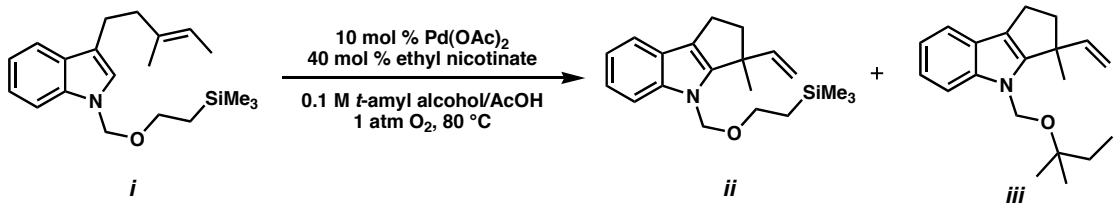
(34) Because the decomposition products were oligomeric, highly polar, and numerous, none were isolated and characterized. Oligomerizations of indole compounds under oxidative conditions have been discussed.[20b]

(35) AcOH has also been used frequently as a solvent in aryl palladation reactions. Therefore, other possible beneficial effects, such as favorable interactions with reaction intermediates, cannot be ruled out.

(36) Other *N*-substituted indoles were not as effective. Acetyl, tosyl, or *tert*-butyldimethylsilyl groups all shut down reactivity. *N*-H indole was prone to heavy decomposition under the reaction conditions. SEM-protected indoles cyclized, but were complicated by an acetalization side reaction (e.g., **i** → **ii** + **iii**).



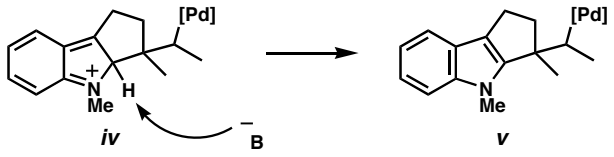
i *ii* *iii*

(37) Interestingly, the mechanism of the oxidative heterocyclization reactions proved to be more complicated than we initially expected, showing a dependence on the nucleophile and the conditions. See Chapter 5 for details of this study.

(38) When AcOH was used as a cosolvent, the yield of the annulated product was lower than when it was not used. Still, only one diastereomer (**297**) was produced even when AcOH was added.

(39) The relative stereochemistry of **297** was confirmed by NOE analysis. See the Experimental Section for details.

(40) It should be noted that it is not clear what the deuterium isotope effect would be in the Wacker-type mechanism, and consequently this result does not necessarily rule out such a pathway. The deprotonation event (**iv** → **v**) would need to be rate-determining in order for an effect to be observed.



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